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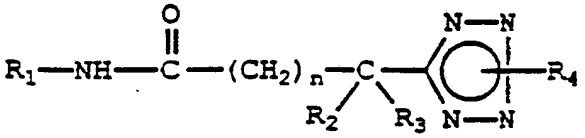

(I)

(57) Abstract

Pharmaceutically useful compounds having ACAT inhibitory activity of formula (I) wherein n is zero, one or two; R_1 is phenyl, substituted phenyl, naphthyl, substituted naphthyl, a heteroaromatic group or a hydrocarbon group having from 1 to 18 carbon atoms; R_2 and R_3 are hydrogen, halo, hydroxy, alkyl, alkenyl, cycloalkyl, phenyl, substituted phenyl, a heteroaryl, or form a spiroalkyl group, and R_4 is a hydrocarbon group having from 1 to 20 carbon atoms.

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AMIDE TETRAZOLE ACAT INHIBITORS

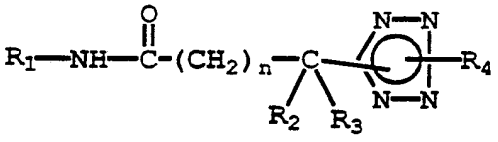
CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of United States Application Serial Number 748,568, filed August 22, 1991.

The present invention describes a series of novel amide tetrazoles which inhibit acyl-CoA: cholesterol acyltransferase (ACAT), the enzyme responsible for the esterification of dietary cholesterol. Such agents may decrease the absorption of dietary cholesterol and therefore provide a therapy for individuals with hypercholesterolemia.

SUMMARY OF THE INVENTION

The compounds of the present invention can be described by the following general formula



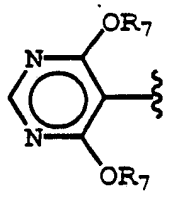
Formula I

wherein n is zero, one or two;
wherein R_1 is selected from
(a) phenyl which is unsubstituted or is substituted with from one to three substituents selected from:
alkyl having from 1 to 4 carbon atoms and which is straight or branched,
alkoxy having from 1 to 3 carbon atoms and which is straight or branched,

alkylthio having from 1 to 3 carbon atoms and which is straight or branched,
phenyl,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
cyano,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and which is straight or branched,
$-(CH_2)_mNR_5R_6$ wherein m is zero or one, and each of R_5 and R_6 is hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;

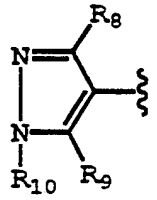
(b) 1- or 2-naphthyl which is unsubstituted or substituted with one to three substituents selected from:
alkyl having from 1 to 4 carbon atoms and which is straight or branched,
alkoxy having from 1 to 3 carbon atoms and which is straight or branched,
hydroxy,
fluorine,
chlorine,
bromine,
nitro,
cyano,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,
$-(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 have the meanings defined above;

(c) the group



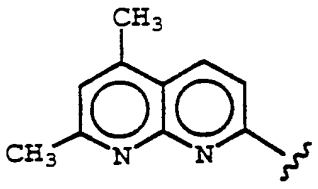
wherein R_7 is a lower alkyl group having from 1 to 3 carbon atoms and is straight or branched;

(d) the group

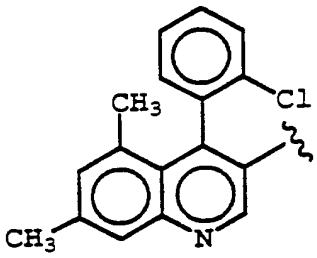


wherein R_8 and R_9 are straight or branched alkyl having from 1 to 4 carbon atoms or phenyl, and R_{10} is a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or two nonadjacent double bonds; phenyl; phenyl substituted with from one to three substituents selected from straight or branched alkyl having 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 3 carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, -COOH, -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched or $(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 are as defined above; or a heterocyclic group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, or 3- or 4-pyridazinyl and the N-oxides thereof;

(e) the group



(f) the group

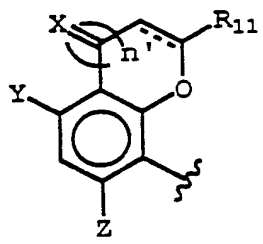


(g) a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or two nonadjacent double bonds;

(h) a cycloalkyl group having from 3 to 8 carbon atoms;

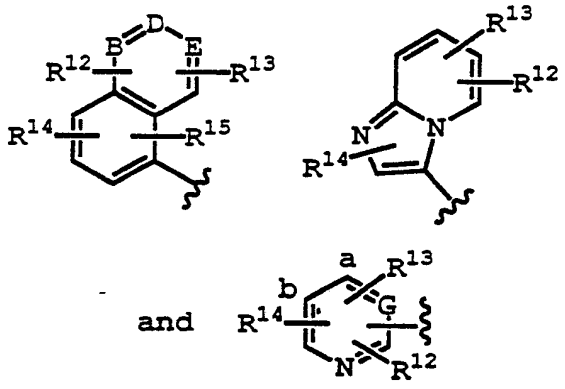
(i) a heteroaromatic group selected from 2-, 3-, or 4-pyridyl which is unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms or 2-, 4-, or 5-pyrimidinyl, and the N-oxides thereof;

(j) the group



wherein --- denotes a single or double bond; Y and Z are each independently hydrogen, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms, or halo; X is oxygen or two hydrogen atoms; R_{11} is hydrogen or a straight or branched alkyl group of 1 to 4 carbon atoms, and n' is zero or one; or

(k) is selected from the group



wherein R^{12}, R^{13}, R^{14}, and R^{15} are each independently hydrogen, halo, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms, an alkylthio group of 1 to 3 carbon atoms, cycloalkylthio of 5 to 7 carbon atoms, phenylalkylthio in which alkyl is 1 to 4 carbon atoms, substituted phenylthio, heteroarylthio, or heteroaryloxy; and B, D, E, and G are nitrogen or carbon where one or more of B, D, and E is nitrogen; with the proviso that when G = N the group is attached to

the nitrogen atom of Formula I at the 4 or 5 position of the pyrimidine ring (a and b),

wherein R_2 and R_3 are the same or different and are selected from:

(a) hydrogen, halo, or one of R_2 or R_3 is hydroxy;

(b) a straight or branched alkyl group having from 1 to 12 carbon atoms, or a cycloalkyl group having from 3 to 8 carbon atoms;

(c) a phenyl or phenylalkyl group where alkyl is from 1 to 4 carbon atoms and which the phenyl ring is unsubstituted or substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, alkythio (straight or branched) having 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, nitro, phenyl, or $(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 have the meanings defined above;

(d) a straight or branched alkenyl group having from 2 to 6 carbon atoms; or

(e) R_2 and R_3 taken together with the carbon atom to which they are attached form an alkylidene group of 1 to 4 carbon atoms, a benzylidene group or a spiroalkyl group having from 3 to 7 carbon atoms;

(f) when R_2 is hydrogen, F, alkyl of C_{1-12} atoms, R_3 can be heteroaryl selected from a 5- or 6-membered monocyclic or fused bicyclic heterocyclic group containing at least 1 to 4 heteroatoms in at least one ring, said heteroatoms being nitrogen, oxygen, or sulfur and combinations thereof, said heterocyclic group being unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms and the N-oxides thereof; or

(g) 1- or 2-naphthyl which is unsubstituted or substituted with one to three substituents selected from:
alkyl having from 1 to 4 carbon atoms and which is straight or branched, and
alkoxy having from 1 to 3 carbon atoms and which is straight or branched,

wherein R_4 is a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and is saturated or is unsaturated and has 1 double bond or has 2 nonadjacent double bonds; or is alkylthio having 1 to 20 carbon atoms and is saturated;
pharmaceutically acceptable salts and individual enantiomeric isomers of the compounds.

DETAILED DESCRIPTION

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention. Suitable acids for forming acid salts of the compounds of Formula I containing a basic group include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The acid addition salts are formed by procedures well known in the art.

Certain compounds of the present invention may also exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the compound. The present invention contemplates all stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Illustrative examples of straight or branched saturated hydrocarbon chains having from 1 to 20 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-undecyl, n-dodecyl, n-hexadecyl, 2,2-dimethyldodecyl, 2-tetradecyl, and n-octadecyl groups.

Illustrative examples of straight or branched hydrocarbon chains having from 1 to 20 carbon atoms and having 1 double bond or 2-nonadjacent double bonds include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl.

Straight or branched alkoxy groups having 1 to 3 carbon atoms include methoxy, ethoxy, n-propoxy, and isopropoxy.

Straight or branched alkyl groups having from 1 to 4 carbon atoms include, for example, methyl, ethyl, n-propyl, isopropyl, and n-butyl.

Cycloalkyl groups having from 3 to 8 carbon atoms which R_1 may represent are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Halo is fluoro, chloro, bromo, or iodo, but preferably fluoro.

A 5- or 6-membered monocyclic or fused bicyclic heterocycle is a monocyclic or fused bicyclic aromatic ring containing at least one to four heteroatoms in at least one ring, such as nitrogen, oxygen, or sulfur or

a combination thereof. Such a heterocyclic group includes, for example, thienyl, benzothienyl, furanyl, benzofuranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, pyrazolyl, isothiazolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, indolyl, quinolinyl, isoquinolinyl, or N-oxides of heterocycles containing a nitrogen atom.

More specifically, such a heterocycle may be a 2- or 3-thienyl; 2-, or 3-furanyl; 2-, or 3-, or 4-pyridyl or 2-, or 3-, or 4-pyridinyl-N-oxide; 2-, 4-, or 5-pyrimidinyl; 3- or 4-pyridazinyl; 2-pyrazinyl; 2-pyrazinyl-N-oxide; 2- or 3-pyrrolyl; 3-, 4-, or 5-pyrazolyl; 2-, 4-, or 5-thiazolyl; 3-, 4-, or 5-isoxazolyl; 2-, 4-, or 5-oxazolyl; 3-, 4-, or 5-isothiazolyl; 5-tetrazolyl; 3- or 5-(1,2,4)-triazolyl; 4- or 5-(1,2,3)-triazolyl; 2-, 4-, or 5-imidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; or 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl.

Preferred compounds of this invention are those wherein the R_4 substituent group is attached to the 2-position of the tetrazole moiety and the side chain or remainder of the molecule is attached to the carbon atom of the tetrazole moiety, the 5-position. Compounds wherein n is zero or one are also preferred with compounds wherein n is zero being more preferred. Compounds wherein R_1 is other than naphthyl or substituted naphthyl are also preferred. Compounds wherein n is zero, R_1 is substituted phenyl, and R_4 is in the 2-position and has from 8 to 18 carbon atoms are most preferred.

Most preferred are compounds of Formula I wherein R_1 is 2,6-(1-methylethyl)phenyl or 2,4,6-trimethoxyphenyl; n is zero; R_2 and R_3 are each independently hydrogen, methyl, fluoro, cyclohexyl, or phenyl, and R_4 is in the 2-position and has 12 carbon atoms.

As shown by the data presented below in Table 1, the compounds of the present invention are potent inhibitors of the enzyme acyl-CoA: cholesterol acyltransferase (ACAT), and are thus effective in inhibiting the esterification and transport of cholesterol across the intestinal cell wall. The compounds of the present invention are thus useful in pharmaceutical formulations for the treatment of hypercholesterolemia or atherosclerosis.

The ability of representative compounds of the present invention to inhibit ACAT was measured using an in vitro test more fully described in F. J. Field and R. G. Salone, Biochemica et Biophysica 712:557-570 (1982). The test assesses the ability of a test compound to inhibit the acylation of cholesterol by oleic acid by measuring the amount of radiolabeled cholesterol oleate formed from radiolabeled oleic acid in a tissue preparation containing rabbit intestinal microsomes (designated IAI) or from rat liver microsomes (designated LAI).

These data appear in Tables 1 and 3 where they are expressed as IC_{50} values; i.e., the concentration of test compound required to inhibit the activity of the enzyme by 50%.

TABLE 1

Example	IAI IC_{50} (μM)
1	0.003
2	0.092
3	0.007
5	0.01
6	0.12
7	0.028
9	0.28
11	0.017
13	0.009
14	0.091
15	0.008
16	0.008
17	0.19
18	0.028
19	0.014
20	0.047
21	0.015
22	0.091
23	0.0075
24	0.041
25	0.80
26	0.079
27	0.014
28	0.018
29	0.010
30	0.77
31	0.27
32	0.053
33	0.017
34	0.069
35	0.009
36	>5
37	0.21

TABLE 1 (cont)

Example	IAI IC_{50} (μM)
44	0.029
45	0.23
46	11
47	2.1
48	0.12
49	0.015
50	1
51	0.66
52	0.036
53	0.097
54	0.22
55	0.026
58	0.031
59	0.049
60	0.028
61	0.31
62	0.014
65	0.015

In one in vivo screen designated APCC, male Sprague-Dawley rats (200 to 225 g) were randomly divided into treatment groups and dosed at 4 PM with either vehicle (CMC/Tween) or suspensions of compounds in vehicle. The normal chow diet was then replaced with a high fat, high cholesterol diet with 0.5% cholic acid. The rats consumed this diet ad libitum during the night and were sacrificed at 8 AM to obtain blood samples for cholesterol analysis using standard procedures. Statistical differences between mean cholesterol values for the same vehicle were determined using analysis of variance followed by Fisher's least significant test. The results of this

trial for representative compounds of the present invention appear in Table 2. The compounds were dosed at 30 mg/kg unless otherwise noted.

TABLE 2

Example	APCC (% ΔTC)
1	-64
2	-32
3	-39
5	-60
6	-37
7	-1
9	-44
11	-41
13	-63
14	-33
15	-66
16	-56
17	-8
18	+15
19	-62
20	-62
21	-61
22	-22
23	-52
24	-56
25	-61
26	-44
27	-69

TABLE 2 (cont)

Example	APCC (% ΔTC)
29	-56
31	-39
32	-47
33	-55
34	-22
35	-60
36	-13
37	-17
44	-66
45	-60
46	+4
47	-4
48	-37
49	-51
50	-34
51	-62
53	-59
54	-43
55	-64
60	-63
61	-64
62	-68

Compounds of Formula I where the side chain is attached directly to a nitrogen atom were also active in the above described tests and the results are shown in Table 3.

TABLE 3

Example	LAI (IC_{50}) (μM)	APCC (% ΔTC)
88	0.010	-62
89	0.390	-35
90	0.10	+5
91	0.006	-68
92	0.015	-77
93	0.022	-30
94	0.029	-26
95	0.058	-64
96	0.19	-47
97	0.056	-69
98	0.021	-65
99	0.032	-51
100	0.080	-63
101	>5.0	+8
102	0.042	-47
103	0.049	-60
104	0.055	-50

In therapeutic use as agents for treating hypercholesterolemia or atherosclerosis, the compounds of Formula I or pharmaceutically acceptable salts thereof are administered to the patient at dosage levels of from 250 to 3000 mg per day. For a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 5 to 40 mg/kg of body weight per day. The specific dosages employed, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being

employed. The determination of optimum dosages for a particular situation is within the skill of the art.

For preparing the pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, and cachets.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers are magnesium dicarbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner cachets are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, or emulsions suitable for oral administration. Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethylcellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of these packaged forms.

The compounds of the present invention can be prepared by various routes all of which are generally known in the art. The compounds of Formula I wherein n is zero, each of R_2 and R_3 is hydrogen and R_1 and R_4 are as defined in Formula I can be prepared as set forth in Chart I hereof.

In Chart I, the tetrazole ester (2) is synthesized via treatment of ethyl cyanoacetate (1) with sodium azide. Alkylation of the tetrazole

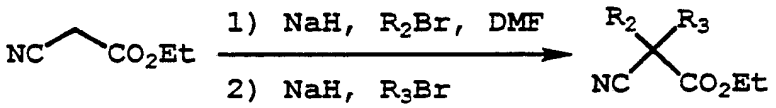
ester (2) with a halide of the formula R_4 halo (3) wherein R_4 has the meaning defined in Formula I and halo is, e.g., bromine or chlorine, provides a mixture of (4) and (7), i.e., the 2- and 1-regioisomers, respectively, isomers which are separable by chromatography. Esters (4) and (7) can then be independently hydrolyzed to the acids (5) and (8) which are coupled with an amine of the formula R_1NH_2 wherein R_1 has the meaning defined in Formula I using carbonyldiimidazole in THF to give the 2 and 1 substituted tetrazole amides (6) and (9), respectively.

Compounds of Formula I wherein n is zero and R_1, R_2, R_3, and R_4 are as defined in Formula I except that both R_2 and R_3 are not hydrogen and R_3 is other than heteroaryl or naphthyl are best synthesized employing the synthetic sequence presented in Chart II. In Chart II the ethyl cyanoacetate derivatives (11) are treated with tri-n-butyltin azide in dioxane at reflux to give compound (12) after acidic hydrolysis with HCl in ether or tetrahydrofuran. The tetrazole is then alkylated with a primary alkyl halide in acetonitrile at reflux using a base such as triethylamine or pyridine. The resulting 2- and 1-regioisomers compounds (13) and (14)] are separated by chromatography. Compound (13) is easily hydrolyzed to carboxylic acid (15) when treated with NaOH or KOH in an alcoholic solvent such as methanol or ethanol at room temperature. However, when R_2 is hydrogen and R_3 is alkyl, aryl, or alkenyl, regioisomer (14) decarboxylates to (17) when subjected to the previously described hydrolytic conditions. The desired acid (19) is obtained under these conditions, however, when $R_2 = R_3 = H$ or R_2 and R_3 is alkyl, alkenyl, aryl, or spirocycloalkyl. The carboxylic

acids (15, 19) are easily converted to the corresponding amides (16, 18) when treated with a coupling agent such as carbonyldiimidazole or dicyclohexylcarbodiimide in tetrahydrofuran or dichloromethane and an appropriate amine. Alternatively, regioisomer (18) is prepared by treating (17) with n-butyllithium in tetrahydrofuran at -20°C followed by the addition of an appropriate isocyanate.

Also when R_2 = H in Compound 15 (Chart II(a)), Compound 15 may be deprotonated using n-BuLi in THF at -78°C to give an anion which can then be treated with an electrophilic reagent (R_2X) to give the α,α'-disubstituted acid shown which can then be coupled with an appropriate amine (R_1NH_2) in a manner as previously described to yield the corresponding amides. Also in Compound 13 (Chart II) when R_2 = H, R_3 as defined in Formula I, this ester can also be deprotonated and the anion fluorinated using N-fluorobenzenesulfonimide to yield the α-fluoro ester which is then used as described in the text for Compound 13.

Compounds of formula (11) are either commercially available or can be synthesized employing the following conditions:



(11)

Ethyl cyanoacetate is treated with one equivalent of sodium hydride in dimethylformamide or tetrahydrofuran followed by the addition of an appropriate alkylating agent such as 1-bromopropane or

benzyl bromide to give monoalkylated analogs of Compound 11. Similarly, a second equivalent of base may then be added followed by the addition of an appropriate alkylating agent to give disubstituted ethyl cyanoacetates of formula (11). The compounds of Formula I wherein n is zero, R_2 is hydrogen, R_3 is heteroaryl, 1- or 2-naphthyl, substituted phenyl, and R_1 and R_4 are as defined in Formula I are prepared as shown in Chart VI hereof wherein the reaction conditions are set forth. Specific Example 38 is illustrative of this synthetic route. The acetonitriles, R_3CH_2CN, are known in the art or are prepared from the alcohol, R_3CH_2OH, by procedures generally known in the art, e.g., J. Am. Chem. Soc. (71):3994, 1949. Spirocycloalkyl analogues are synthesized in a similar manner by employing dihalo alkyl halides of the formula halo-$(CH_2)_p$-halo wherein p is two to six and halo is chlorine or bromine as the alkylating agent. An illustrative alkylating agent is 1,4-dibromobutane. Compounds of Formula I wherein n = zero, R_2, R_3 = alkyl, aryl, R_1, R_4 as defined in Formula I can also be synthesized as shown in Chart XI. The commercially available acetonitriles are treated with tri-n-butyltin azide in dioxane at reflux to give the corresponding tetrazole which is then alkylated with a primary alkyl halide in acetonitrile at reflux using a base such as TEA or pyridine. The resulting 1- and 2-regioisomers are separated by chromatography. Treatment of these compounds with n-butyllithium in tetrahydrofuran at -78°C followed by the addition of an appropriate isocyanate (R_1NCO) gives the desired amides. Specific Example 46 is illustrative of this synthetic route.

Additionally compounds of Formula I wherein n = zero, R_2, and/or R_3 is F or OH, R_1, R_4 as defined

in Formula I can be synthesized as shown in Chart XII. The alkylated tetrazole is treated with n-BuLi and TMEDA in THF at -78°C followed by ethyl phenyl glyoxylate. The resulting hydroxy compound was then treated with diethyl amino sulfur trifluoride (DAST) in dichloromethane at -78°C under N_2. The resulting fluoro ester was then hydrolyzed using NaOH in methanol/water. The resulting acid was converted to the acid chloride via treatment with oxalyl chloride in dichloromethane at room temperature. The crude acid chloride was treated with an appropriate amine in dichloromethane with Et_3N as base at 0°C to yield the desired amide. Specific Example 65 is illustrative of this synthetic route. Also the hydroxyester may be treated with t-butyldimethyl silyl trifluoromethane sulfonate in dichloromethane with Et_3N as base to yield the protected hydroxy ester, which can then be converted to the desired amide as shown in the scheme.

The compounds of Formula I wherein n is one or two, R_2 and R_3 are hydrogen and R_1 and R_4 are as defined in Formula I are prepared as set forth in Chart III hereof. In Chart III an appropriate nitrile ester (20) is heated with an alkali metal azide, such as LiN_3 or NaN_3, and NH_4Cl in dimethylformamide at temperatures ranging from 50° to 80°C to give after work-up the corresponding tetrazole ester (20-A). The tetrazole ester (20-A) is heated, typically at temperatures between 50° and 100°C, with a tertiary amine such as triethylamine, and an appropriate alkyl halide, including alkyl bromides, chlorides, and iodides, or an arylalkyl halide in a polar solvent, such as CH_3CN, to give after work-up and chromatographic separation both of the corresponding regioisomeric 1-alkylated and 2-alkylated tetrazole esters (22) and (21). The alkyl tetrazole esters (21

and 22) are stirred, typically at temperatures between 0° and 30°C, with alkali metal hydroxides, such as LiOH, NaOH, or KOH, in an alcoholic solvent such as methanol or ethanol for 1 to 24 hours to give after work-up the corresponding alkyltetrazole carboxylic acids (23 and 24). The alkyltetrazole carboxylic acids are coupled with primary amines, especially aryl amines of the formula R_1NH_2 wherein R_1 is as defined in Formula I such as 2,4,6-trimethoxyaniline, 2,6-diisopropylaniline, and 2,4-difluoroaniline, using a carboxylic acid activating reagent such as carbonyldiimidazole or dicyclohexylcarbodiimide in an aprotic solvent such as THF or CH_2Cl_2, at temperatures between -10° and +110°C to give after work-up the corresponding alkyltetrazole amides (25 and 26).

The compounds of general Formula I wherein n is one, R_2 is hydrogen, R_3 is phenyl, substituted phenyl, heteroaryl, alkyl, or alkenyl and R_1 and R_4 are as defined in Formula I are prepared as set forth in Chart IV. In Chart IV the group $R_3(X)$ is phenyl, substituted phenyl or heteroaryl as defined in Formula I or $R_3(X)$ is a straight or branched alkyl having from 1 to 6 carbon atoms or a straight or branched alkenyl having from 2 to 6 carbon atoms. The ß-substituted cyanopropionic acid compound (27) is prepared from the corresponding aldehyde of the formula XCHO using the procedure described in US 4,760,089. Compound (27) is treated with an appropriate amine, R_1NH_2 wherein R_1 has the meaning defined in general Formula I employing a coupling agent such as carbonyldiimidazole in tetrahydrofuran at room temperature or dicylohexylcarbodiimide in dichloromethane at 0°C to give the nitrile amide (28). The nitrile amide (28) is converted to the tetrazole (29) by treatment with $(n\text{-}Bu)_3SnN_3$ in refluxing

dioxane and then is alkylated with an appropriate compound of the formula R_4halo wherein R_4 has the meaning defined in Formula I and halo is chlorine, or bromine employing triethylamine in acetonitrile. The products (30) and (31) are separated by chromatography. Specific Example 45 is illustrative of this synthetic route.

The compounds of Formula I wherein n is two, R_2 is hydrogen, and R_3 is phenyl or substituted phenyl are prepared as set forth in Chart V. Compound (32) is prepared according to the method of Paganelli (Tett. Lett. 32:2807-2810, 1991) by a transition metal catalyzed Michael addition of benzyl cyanide to methyl acrylate. Compound (32) is then treated with $(n\text{-}Bu)_3SnN_3$ in refluxing dioxane to give the tetrazole (33), which is then alkylated with an alkyl halide, R_4halo, e.g., R_4Br, wherein R_4 is as defined in Formula I, in acetonitrile employing Et_3N as base, giving a mixture of regioisomers (34) and (35) which are separated by flash chromatography. Hydrolysis of each ester with ethanolic NaOH at room temperature gives the respective acids (36) and (38). The acids are then coupled with an appropriate amine of the formula R_1NH_2 wherein R_1 is as defined in Formula I employing carbonyldiimidazole in tetrahydrofuran at room temperature or dicyclohexylcarbodiimide in CH_2Cl_2 at 0°C as coupling agent to give the amides (37) and (39).

The compounds of Formula I wherein n is one, R_3 is other than heteroaryl and R_1, R_2, and R_4 are as defined in Formula I are prepared as set forth in Chart VII.

Ethyl cyanoacetate is alkylated (or dialkylated) by treatment with NaH in an appropriate solvent such as dimethylformamide or tetrahydrofuran at from 0° to

25°C to give the alkylated nitrile (40). The nitrile is then treated with $(n\text{-}Bu)_3SnN_3$ in dioxane at reflux for 24 hours to give after acidic hydrolysis the tetrazole (41) which is then alkylated with an alkyl halide (R_4Br) in CH_3CN employing Et_3N as base to give a mixture of regioisomers (42) and (43). The regioisomers are separated by flash chromatography and each ester is reduced by DIBAL-H in CH_2Cl_2 or toluene at -78°C to give the corresponding alcohols (44) and (45). The alcohols are treated with methanesulfonyl chloride in CH_2Cl_2 using triethylamine as a base at 0°C to give the corresponding mesylates which are then treated with KCN in dimethylformamide or dimethyl sulfoxide at 100°C to give the corresponding nitriles (46) and (47). These are then hydrolyzed to the corresponding acids (48) and (49) by treatment with ethanolic NaOH (or KOH) at reflux. The acids are then coupled with an appropriate amine employing carbonyldiimidazole in tetrahydrofuran at room temperature or dicyclohexylcarbodiimide in CH_2Cl_2 at 0°C to give the amides (50) and (51).

The compounds of Formula I wherein n is one, R_3 is heteroaryl and R_1 and R_4 are as defined in Formula I are prepared in the same manner as set forth in Chart VII beginning with compounds which are the same as compounds (42) and (43) except that R_2 is hydrogen and R_3 is heteroaryl. These comparable tetrazole intermediates are prepared as set forth in Chart VIII hereof wherein R_3 is heteroaryl and R_4 has the meaning defined in Formula I. The reaction conditions are set forth in Chart VIII.

The compounds of Formula I wherein n is two, R_2 and R_3 are as defined in Formula I only at least one is other than hydrogen, and R_1 and R_4 are as defined in Formula I are prepared as set forth in Chart IX.

Malonitrile is alkylated (or dialkylated) by treatment with NaH in an appropriate solvent such as dimethylformamide or tetrahydrofuran at 0° to 25°C to give compounds (51). Treatment of the substituted nitrile with $(n\text{-}Bu)_3SnN_3$ in refluxing dioxane for 24 hours gives, after acidic hydrolysis, the tetrazole (52), which is then alkylated with an alkyl halide (R_4Br) in CH_3CN employing Et_3N as base to give a mixture of regioisomers (53) and (54). The regioisomers are then separated by flash chromatography and each nitrile is then reduced to the corresponding aldehydes (55) and (56) by treatment with Raney nickel in formic acid at 60°C. The resulting aldehydes are then treated with a stabilized ylide such as ethyl(triphenylphosphoranylidene)acetate in CH_2Cl_2 at room temperature to give (57) and (58) which are reduced catalytically using hydrogen gas, Pd/C as catalyst in methanol or ethanol at room temperature to give esters (59) and (60). These are then hydrolyzed to the corresponding acids (61) and (62) by treatment with alcoholic (MeOH/EtOH) alkali metal hydroxide (NaOH or KOH) at reflux. The acids are then coupled with an appropriate amine employing carbonyldiimidazole in tetrahydrofuran at room temperature or dicyclohexylcarbodiimide in CH_2Cl_2 at 0°C to give amides (63) and (64).

The N-oxides of compounds of this invention are prepared by standard procedures known in the art, for example, by treatment with m-perchlorobenzoic acid at reflux in chloroform or dichloromethane.

The isocyanates, R_1NCO, and the amines R_1NH_2 wherein R_1 has the meaning defined in Formula I, employed in preparing the compounds of this invention are known in the art or can be prepared by procedures generally known in the art. For example, the pyrazole

amines are prepared as set forth in Chart X hereof wherein the reaction conditions are indicated in the chart.

In addition, compounds of Formula I having an asymmetric carbon atom can be synthesized in either enantiomeric form (R_2 does not equal R_3) by treating compounds (15) or (19) in Chart II, (27) in Chart IV, (36) or (38) in Chart V, (48) or (49) in Chart VII, and (61) or (62) in Chart IX with appropriate chiral amines such as R-(+)- or S-(-)-α-methylbenzyl amine, (1S, 2R) ephedrine, or brucine. The salts are prepared by dissolving the racemic acid enumerated above in ethyl acetate or a mixture of hexane/ethyl acetate containing the appropriate chiral amine. The chiral salt is collected by filtration and recrystallized several times from hexane/ethyl acetate. The chiral acid is then liberated through an acidic workup and its enantiomeric purity is determined by chiral HPLC. The chiral acids are then coupled with appropriate amines to give enantiomerically pure compounds designated as (16), (18), (28), (37), (39), (50), (51), (63), and (64), respectively. Similarly, to obtain the chiral products of the compounds of formulas (67) and (68) in Chart VI the intermediates (65) and (66) are treated with n-BuLi and ethyl chloroformate as shown in Chart VIII and the resulting esters are hydrolyzed to obtain acids corresponding to (48) and (49) only wherein R_4 is a heteroaryl group. These acids are then treated with chiral amines as described above.

For compounds of Formula I where the side chain is attached on a nitrogen atom of the tetrazole ring (Chart XIII), a nitrile (R_4CN) is converted to the corresponding 5-substituted tetrazole by cycloaddition

with an azide (ammonium azide, tributyltin azide, etc) in an inert solvent such as dimethylformamide. The resulting 5-substituted tetrazole can be alkylated with an α-bromo ester using a base such as triethylamine in a neutral solvent such as acetonitrile. The resulting mixture of 1,5 and 2,5 regioisomers is separated by chromatography or recrystallization. The esters of the pure regioisomers are then individually saponified using an inorganic base (NaOH, KOH, etc) and acidified with a mineral acid such as HCl to give the corresponding carboxylic acids. The carboxylic acids are coupled with various amines using standard coupling reagents (CDI, DCC, mixed anhydride, etc) to give the final products.

EXAMPLE 1

N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-2H-tetrazole-5-acetamide (R_1 = 2,6-diisopropylphenyl; n is zero; R_2 and R_3 are hydrogen; and R_4 is 2-$(CH_2)_{11}CH_3$.

(a) Tetrazoleacetic acid ethyl ester

To a solution of ethylcyanoacetate (20.0 g, 0.177 mol) in dimethylformamide (DMF) (180 mL) was added NH_4Cl (10.4 g, 0.19 mol) and sodium azide (12.6 g, 0.19 mol) sequentially. The mixture was heated for 5 hours at 100°C, allowed to cool, and the DMF removed in vacuo. The residue was taken up in water (150 mL), acidified to pH 2 with concentrated HCl, and filtered. The filtrate was cooled to 5°C and allowed to crystallize. The solid was filtered, dried in vacuo over self-indicating silica gel to give 10.61 g, 42%, mp 124-129°C.

(b) 1-Dodecyltetrazoleacetic acid ethyl ester and 2-Dodecyltetrazole acetic acid ethyl ester

1-Bromododecane (8.78 g, 0.035 mol) was added to a refluxing solution of the tetrazole acetic acid ethyl ester (5.0 g, 0.032 mol) obtained in (1a) above, and triethylamine (3.56 g, 0.035 mol) in acetonitrile (150 mL). The mixture was refluxed for 18 hours, allowed to cool, and filtered. The filtrate was concentrated in vacuo and partitioned between ethyl acetate (150 mL) and water (150 mL). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$, then filtered, concentrated, and chromatographed on silica gel, eluting with 10%, then 20% ethyl acetate in hexanes to give 5.40 g, 52% of the 2-isomer (Rf 0.66, 50% ethyl acetate/hexane) as an oil and 3.39 g, 33% of the 1-isomer (Rf 0.50, 50% ethyl acetate/hexane) as a solid, mp 59-62°C.

(c) 2-Dodecyltetrazoleacetic acid

A solution of KOH (4.21 g, 0.075 mol) in water (10 mL) was added to a solution of the 2-dodecyltetrazole acetic acid ethyl ester (23.2 g, 0.0715 mol) in ethanol (250 mL). The mixture was stirred at room temperature for 3 hours, concentrated in vacuo to ~50 mL, diluted with water (200 mL), and washed with ethyl acetate (100 mL). The aqueous layer was acidified with 1.0 M HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 18.0 g, 85% of a white solid, mp 70-73°C.

(d) N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-2H-tetrazole-5-acetamide

Carbonyldiimidazole (5.74 g, 0.035 mol) was added to a solution of the 2-dodecyltetrazole acetic acid (10.0 g, 0.034 mol) obtained in (c) above in dry THF (100 mL) under an inert atmosphere (N_2). The mixture

was stirred at room temperature for 30 minutes, then 2,6-diisopropylaniline (6.7 mL, 0.038 mol) was added in one portion. The resulting solution was stirred for 3 days at room temperature, concentrated in vacuo, taken up in dichloromethane (200 mL), washed with water (100 mL) and brine (100 mL), and dried over Na_2SO_4. The dried solution was filtered, concentrated, and chromatographed on silica gel, eluting with 15% ethyl acetate in hexanes to give 10.6 g, 68% of the title compound as an off-white solid, mp 75-79°C.

EXAMPLE 2

N-[2,6-Bis(1-methylethyl)phenyl]-1-dodecyl-1H-tetrazole-5-acetamide (R = 2,6-diisopropylphenyl; n is zero; R_2 and R_3 are hydrogen; and R_4 is $1-(CH_2)_{11}CH_3$.

Following the procedure set forth in steps (c) and (d) of Example 1, only substituting 1-dodecyl-tetrazoleacetic acid ethyl ester for 2-dodecyl-tetrazoleacetic acid ethyl ester, the title compound was obtained, mp 88-91°C.

Following the general procedure of Examples 1 and 2 only substituting an appropriate amount of the amine listed below for 2,6-diisopropylaniline, the respective products listed below were obtained.

Example	Amine	Product
3	4,6-dimethoxy-pyrimidin-5-ylamine	N-(4,6-dimethoxy-5-pyrimidinyl)-2-dodecyl-2H-tetrazole-5-acetamide
4	4,6-dimethoxy-pyrimidine-5-ylamine	N-(4,6-dimethoxy-5-pyrimidinyl)-2-dodecyl-1H-tetrazole-5-acetamide
5	2,4,6-trimethoxy-aniline	2-dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, mp 117-118°C.
6	2,4,6-trimethoxy-aniline	1-dodecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-5-acetamide, mp 108-109.5°C.
7	3-methylpyridin-2-ylamine	2-dodecyl-N-(3-methyl-2-pyridinyl)-2H-tetrazole-5-acetamide, mp 63-65°C.
8	3-methylpyridin-2-ylamine	1-dodecyl-N-(3-methyl-2-pyridinyl)-1H-tetrazole acetamide
9	2,4-difluoroaniline	N-(2,4-difluoro-phenyl)-2-dodecyl-2H-tetrazole-5-acetamide, mp 79-80°C.
10	2,4-difluoroaniline	N-(2,4-difluoro-phenyl)-1-dodecyl-1H-tetrazole-5-acetamide
11	1,3,5-trimethyl-1H-pyrazol-4-ylamine	2-dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide, mp 95-97°C.

Example	Amine	Product
12	1,3,5-trimethyl-1H-pyrazol-4-ylamine	1-dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-tetrazole-5-acetamide

The compounds of Example 9 and 10 above were made as a mixture.

EXAMPLE 13

(±) 2-Dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

(a) (±) α-Phenyl tetrazole-5-acetic acid, ethyl ester

Ethyl phenylcyanoacetate (44.4 g; 0.23 moles) was dissolved in p-dioxane (900 mL) and treated with n-tributyltin azide (76.3 g; 0.23 moles) in one portion. The solution was heated to reflux for 16 hours, cooled to room temperature, and then concentrated in vacuo. The resulting liquid was dissolved in ethyl ether (500 mL) and treated with gaseous HCl for over 15 minutes. The ether was removed in vacuo leaving a viscous liquid which solidified when triturated with boiling hexanes.
Yield: 47.29 (88%).
^{1}H NMR (DMSO-D_6) δ 7.3 (s, 5H), 5.7 (s, 1H), 4.2 (q, 2H), 1.1 (t, 3H) ppm.

(b) (±) 2-Dodecyl-α-phenyl-2H-tetrazole-5-acetic acid, ethyl ester

The tetrazole ester (a) (47 g; 0.20 moles) was dissolved in acetonitrile (550 mL) containing one equivalent of triethylamine (20.2 g; 0.20 moles). The solution was heated to reflux and then 1-bromododecane (49.8 g; 0.20 moles) was added dropwise over 20 minutes. Upon completion, the solution was heated

to reflux for 16 hours, cooled to room temperature, and concentrated in vacuo. The residue was triturated with ethyl acetate (1 L), filtered, and the filtrate was washed with aqueous HCl (1N), brine, and dried over magnesium sulfate. The drying agent was removed by filtration and the solvent concentrated in vacuo, leaving a viscous liquid containing both 1- and 2-isomers. The regioisomers were separated by silica gel chromatography using 75% hexane and 25% ethyl acetate as the eluent, obtaining the title compound as a colorless liquid. Yield: 33 g (41%).
^{1}H NMR ($CDCl_3$) δ 7.5 (d, 2H), 7.3 (m, 3H), 5.3 (s, 1H), 4.5 (t, 2H), 4.2 (m, 2H), 2.0 (m, 2H), 1.2 (s, 18H), 0.8 (t, 3H) ppm.

(c) (±) 1-Dodecyl-α-phenyl-1H-tetrazole-5-acetic acid, ethyl ester

The 1-dodecyl compound was isolated from the silica gel column previously described in isolating compound (b) above. Yield: 14.3 g (18%).
^{1}H NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 5.3 (s, 1H), 4.2 (q, 2H), 4.0 (t, 2H), 1.5 (m, 2H), 1.2 (s, 18H), 0.8 (t, 3H) ppm.

(d) (±) 2-Dodecyl-α-phenyl-2H-tetrazole-5-acetic acid

Compound (c) (33.0 g; 0.082 moles) obtained above was dissolved in absolute ethanol (400 mL) and treated with sodium hydroxide pellets (6.5 g; 0.16 moles) in one portion. The solution was stirred for several hours at room temperature before concentrating the ethanol in vacuo, leaving a viscous syrup. The carboxylic acid sodium salt was dissolved in water (300 mL) and washed with one portion of ethyl ether (75 mL). The aqueous solution was then acidified to a pH of 1.0 with concentrated HCl, and the product was extracted with two portions of ethyl acetate. The combined organic solution was washed once with brine,

dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, leaving a colorless liquid that solidified on standing, mp 55-57°C. Yield: 27.8 g (91%).

^1H NMR (DMSO-D_6) δ 7.4 (d, 2H), 7.3 (m, 3H), 5.4 (s, 1H), 4.6 (t, 2H), 1.8 (m, 2H), 1.2 (s, 18H), 0.8 (s, 3H) ppm.

(e) (±) 2-Dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

The compound obtained in (d) above (6.58 g; 17.6 mmoles) was dissolved in tetrahydrofuran (50 mL), treated with carbonyldiimidazole (3.1 g; 19.1 mmoles), and stirred for 1 hour at room temperature under an atmosphere of N_2. A solution of 2,4,6-trimethoxyaniline (3.2 g; 17.6 mmoles/50 mL THF) was then added in one portion and the solution was stirred at room temperature for overnight. Ethyl acetate (150 mL) was then added as well as aqueous HCl (1N). The layers were separated and the organic portion was washed with NaOH (1N), brine, and then dried over $MgSO_4$. The drying agent was filtered and the filtrate concentrated in vacuo leaving a lavender colored solid which was purified by silica gel chromatography using chloroform (95%)/methanol (5%) as the eluent. Yield: 6.7 g (70%), mp 119-120°C.

When in the procedure of Example 13(e) an appropriate amount of the amine listed below was substituted for 2,4,6-trimethoxyaniline and the general procedure of Example 13(e) was followed, the respective products listed below were obtained.

Example	Amine	Product
14	Aniline	(±)-2-dodecyl-N,α-diphenyl-2H-tetrazole-5-acetamide, mp 74-76°C
15	2,6-diisopropyl-aniline	(±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 7.9 (s, 1H), 7.5 (d, 2H), 7.4 (m, 3H), 7.2 (t, 1H), 7.1 (d, 2H), 5.5 (s, 1H), 4.6 (t, 2H), 2.8 (m, 2H), 2.0 (m, 2H), 1.3 (s, 18H), 1.0 (d, 12H), 0.8 (t, 3H) ppm.
16	4,6-dimethoxy-pyrimidin-5-ylamine	(±)-N-(4,6-dimethoxy-5-pyrimidinyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 1H), 7.9 (bs, 1H), 7.5 (d, 2H), 7.3 (q, 3H), 5.4 (s, 1H), 4.6 (t, 2H), 3.9 (s, 6H), 2.0 (m, 2H), 1.3 (s, 18H), 0.8 (t, 3H) ppm.
17	5,7-dimethyl-1,8-naphthyridine-2-ylamine	(±)-N-(5,7-dimethyl-1,8-naphthyridine-2-yl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide, mp 148-149°C.
18	3-amino-4-(2-chlorophenyl)-6,8-dimethyl quinoline	(±)-N-[4-(2-chloro phenyl)-6,8-dimethyl-3-quinolinyl]-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 7.1-7.6 (m, 11H), 5.6 (s, 1H), 4.6 (tr, 2H), 2.8 (s, 3H), 2.3 (s, 3H), 1.9 (tr, 2H), 1.2 (s, 18H), 0.9 (m, 3H) ppm.

Example	Amine	Product
19	1,3,5-trimethyl-1H-pyrazol-4-ylamine	(±)-2-dodecyl-α-phenyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 7.7 (bs, 1H), 7.4 (d, 2H), 7.2 (m, 4H), 5.4 (s, 1H), 4.6 (t, 3H), 3.6 (s, 3H), 2.0 (d, 6H), 1.3 (s, 18H), 0.8 (t, 3H) ppm.
20	cyclopropylamine	(±)-N-cyclopropyl-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 7.3-7.4 (m, 5H), 6.7 (bs, 1H), 5.2 (s, 1H), 4.6 (s, 3H), 2.7 (m, 1H), 2.0 (m, 2H), 1.3 (s, 18H), 0.8 (t, 3H), 0.7 (m, 2H), 0.4 (m, 2H) ppm.
21	2,4-difluoroaniline	(±)-N-(2,4-difluoro-phenyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 8.9 (bs, 1H), 8.3 (m, 1H), 7.5 (dd, 2H), 7.4 (m, 3H), 6.9 (m, 2H), 5.4 (s, 1H), 4.6 (t, 2H), 2.0 (m, 2H), 1.2 (s, 18H), 0.8 (t, 3H) ppm.
22	2-pyridinylamine	(±)-2-dodecyl-α-phenyl-N-2-pyridinyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 9.0 (bs, 1H), 8.2 (m, 2H), 7.6 (t, 1H), 7.5 (d, 2H), 7.3 (m, 3H), 7.0 (m, 1H), 5.4 (s, 1H), 4.6 (t, 2H), 2.0 (m, 2H), 1.3 (s, 18H), 0.8 (t, 3H) ppm.

Example	Amine	Product
23	3-methylpyridin-2-ylamine	(±)-2-dodecyl-N-(3-methyl-2-pyridinyl)-α-phenyl-2H-tetrazole-5-acetamide, ^{1}H NMR ($CDCl_3$) δ 8.7 (bs, 1H), 8.2 (d, 1H), 7.5 (t, 3H), 7.3 (q, 3H), 7.0 (m, 1H), 5.5 (s, 1H), 4.6 (t, 2H), 2.1 (s, 3H), 2.0 (m, 2H), 1.3 (s, 18H), 0.8 (t, 3H) ppm.

EXAMPLE 24

(±)-2-Dodecyl-N-(3-methyl-2-pyridinyl)-2-phenyl-2H-tetrazole-5-acetamide, N-oxide

The compound of Example 23 (0.50 g; 1.0 mmole) was dissolved in dichloromethane and then treated with MCPBA (0.22 g; 1.1 mmole) in one portion and stirred at room temperature for 12 hours. The resulting 3-chlorobenzoic acid byproduct was removed by washing the organic solution with aqueous potassium carbonate and then brine. The dichloromethane was dried over magnesium sulfate, filtered, and concentrated in vacuo, leaving a white precipitate. The crude product was triturated with ethyl ether and collected by filtration.

^{1}H NMR ($CDCl_3$) δ 9.7 (bs, 1H), 8.1 (d, 1H), 7.6 (d, 2H), 7.3 (q, 3H), 7.1 (d, 1H), 7.0 (t, 1H), 5.5 (s, 1H), 4.6 (t, 2H), 2.2 (s, 3H), 2.0 (m, 2H), 1.3 (s, 18H), 0.8 (t, 3H) ppm.

EXAMPLE 25

(±)-N-(2,4-Difluorophenyl)-1-dodecyl-α-phenyl-1H-tetrazole-5-acetamide

(a) 5-Benzyl-1-dodecyl-1H-tetrazole

(±)-1-Dodecyl-α-phenyl-1H-tetrazole-5-acetic acid, ethyl ester, i.e., the compound of Example 13(c) (14 g; 0.034 mmoles) was dissolved in absolute ethanol (175 mL) and treated with sodium hydroxide pellets (2.7 g; 0.069 mmoles). The solution was stirred for 30 minutes forming a gelatinous precipitate. The solid was removed by filtration, dissolved in water, and then acidified to a pH of 1.0 using concentrated HCl. The precipitate was collected by filtration and washed with water. Yield: 8.5 g (76%), mp 50-51°C.

(b) (±)-N-(2,4-Difluorophenyl)-1-dodecyl-α-phenyl-1H-tetrazole-5-acetamide

The compound from (a) above (1.5 g; 4.5 mmoles) was dissolved in tetrahydrofuran (20 mL), cooled to -20°C, and then treated dropwise with n-butyllithium (2.8 mL; 4.5 mmoles) for over 5 minutes. The solution was stirred for 5 minutes before adding 2,4-difluorophenyl isocyanate (0.7 g; 4.5 mmoles). The ice bath was removed and the solution gradually warmed to room temperature over 30 minutes, at which time the reaction was quenched with water (20 mL) and diluted with ethyl acetate. The layers were separated and the organic portion was washed with aqueous HCl (1N), aqueous sodium carbonate (10%), and brine. The solution was dried over magnesium sulfate, filtered, and stripped to dryness leaving a viscous liquid that was dissolved in 75% hexane/25% ethyl acetate and chromatographed using silica gel. Yield: 0.9 g (41%).

^{1}H NMR ($CDCl_3$) δ 10.1 (s, 1H), 8.1 (m, 1H), 7.3 (s, 5H), 6.8 (m, 2H), 5.2 (s, 1H), 4.2 (t, 2H), 1.6 (m, 2H), 1.2 (d, 18H), 0.8 (t, 3H) ppm.

EXAMPLE 26

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-1-dodecyl-α-phenyl-1H-tetrazole-5-acetamide

When in the procedure of Example 25(b) an appropriate amount of 2,6-diisopropylphenylisocyanate was substituted for 2,4-difluorophenylisocyanate and the general procedure of Example 25(b) was followed, the title compound was obtained, mp 113-115°C.

EXAMPLE 27

2-Dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

(a) Ethyl 2,2-dimethylcyanoacetate

A solution of ethyl cyanoacetate (20 g; 0.17 moles) in tetrahydrofuran (350 mL) was cooled to -10°C followed by the addition of sodium hydride (7.25 g; 0.17 moles) in several portions. The suspension was stirred for 10 minutes at -10°C before adding iodomethane (23.3 g; 0.17 moles). The ice bath was removed and the solution gradually warmed to 20°C for over 45 minutes. The solution was then recooled to -10°C and a second equivalent of sodium hydride (7.25 g; 0.17 moles) was added, again, in small portions. Soon after, iodomethane (23.3 g; 0.17 moles) was added, the ice bath removed, and the solution stirred at room temperature for 2 hours before being quenched with H_2O. The product was extracted with ethyl ether (500 mL) and washed with brine, dried over $MgSO_4$, and the solution concentrated in vacuo, leaving a crude product that was purified by distillation. Yield: 16.9 g, b.p. 82-85°C; 15 mm Hg.

(b) α,α′-Dimethyltetrazole-5-acetic acid, ethyl ester

Ethyl-2,2-dimethylcyanoacetate (a) (11.6 g; 0.082 moles) was dissolved in dioxane (240 mL) and treated with tri-n-butyltin azide (76.3 g; 0.23 moles) in one portion. The solution was refluxed for overnight, cooled to room temperature, and then concentrated in vacuo. The resulting liquid was dissolved in ethyl ether (500 mL) and treated with gaseous HCl continuously for 15 minutes. The ether was concentrated in vacuo, leaving a viscous liquid which gradually solidified on standing. Yield: 8.4 g.

^{1}H NMR ($CDCl_3$) δ 12.2 (bs, 1H), 4.2 (q, 2H), 1.8 (s, 6H), 1.3 (5, 3H) ppm.

(c) 2-Dodecyl-α,α′-dimethyl-2H-tetrazole-5-acetic acid, ethyl ester

The compound obtained in (b) above (4.0 g; 0.021 moles) was dissolved in acetonitrile (50 mL) containing one equivalent of triethylamine (2.3 g; 0.021 moles). The solution was heated to reflux followed by the addition of 1-bromododecane (5.6 g; 0.022 moles). The solution was refluxed for 16 hours, cooled to room temperature, and then concentrated in vacuo. The residue was triturated with ethyl acetate (250 mL), filtered, and the filtrate was washed with aqueous HCl (1N), brine, and dried over magnesium sulfate. Concentration of the solution after filtration afforded a viscous liquid containing both the 1- and 2-regioisomers. The latter isomer was obtained by silica gel chromatography using 75% hexane and 25% ethyl acetate as the eluant. The product was isolated as a colorless liquid (4.5 g).

^{1}H NMR ($CDCl_3$) δ 4.5 (t, 2H), 4.1 (q, 2H), 1.9 (m, 2H), 1.7 (s, 6H), 1.2 (s, 18H), 0.9 (t, 3H) ppm.

(d) 2-Dodecyl-α,α'-dimethyl-2H-tetrazole-5-acetic acid

The compound obtained in (c) above (3.2 g; 0.009 moles) was dissolved in absolute ethanol (40 mL) and treated with sodium hydroxide pellets (.38 g; 0.0095 moles) in one portion. The solution was stirred at room temperature for overnight before concentrating the ethanol in vacuo. The residue was dissolved in H_2O and acidified to a pH of 1.0. The product was extracted with ethyl acetate in two portions. The combined organic solution was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated in vacuo leaving a colorless liquid that solidified on standing. Yield: 2.05 g.

^1H NMR ($CDCl_3$) δ 4.5 (t, 2H), 2.0 (m, 2H), 1.7 (s, 6H), 1.2 (s, 18H), 0.9 (t, 3H) ppm.

(e) 2-Dodecyl-α,α'-dimethyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide

The carboxylic acid obtained in (d) above (2.0 g; 0.006 moles) was dissolved in dry THF (50 mL) and then treated with carbonyldiimidazole (1.0 g; 0.006 moles) in one portion. The solution was stirred for 1 hour under nitrogen before adding 2,4,6-trimethoxyaniline (1.0 g; 0.006 moles), also in one portion. The solution was stirred for 5 days under nitrogen and at room temperature. The solution was diluted with ethyl acetate and washed with aqueous HCl (1N), NaOH (1N), and brine. Magnesium sulfate was added as the drying agent and the solution filtered. The filtrate was concentrated in vacuo leaving a maroon-colored liquid. The crude product was purified by silica gel chromatography employing 75% hexane and 25% ethyl acetate as the eluant. Yield: 1.5 g colorless liquid.

^{1}H NMR ($CDCl_3$) δ 7.2 (bs, 1H), 6.1 (s, 2H), 4.6 (t, 2H), 3.7 (d, 9H), 2.1 (m, 2H), 1.7 (s, 6H), 1.3 (s, 18H), 0.9 (t, 3H) ppm.

EXAMPLE 28

2-Dodecyl-α,α'-(2-propenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

Following the general procedure of Example 27, only substituting ethyl-2,2-bis(allyl)cyanoacetate for ethyl-2,2-dimethylcyanoacetate in 27(a) and following the general procedure of 13(a) through 13(e) the title compound was obtained.

^{1}H NMR ($CDCl_3$) δ 8.5 (bs, 1H), 6.1 (s, 2H), 5.7 (m, 2H), 5.0 (m, 4H), 4.6 (t, 2H), 3.7 (d, 9H), 3.0 (dd, 2H), 2.9 (dd, 2H), 1.9 (m, 2H), 1.2 (s, 18H), 0.8 (t, 3H) ppm.

EXAMPLE 29

1-(2-Dodecyl-2H-tetrazol-5-yl)-N-(2,4,6-trimethoxyphenyl)cyclopentanecarboxamide

(a) 1,1-Dicyanocyclopentane

Sodium hydride (37.8 g; 0.94 moles) was suspended in dimethylformamide (250 mL) under an atmosphere of N_2. A solution of malononitrile (30 g; 0.45 moles) and 1,4-dibromobutane 99.7 g; 0.45 moles) in dimethylformamide (150 mL) was added dropwise at such a rate so as not to exceed 30°C. The mixture was stirred for overnight, poured into H_2O (500 mL), and then washed with two portions of ethyl ether. The organics were combined, washed with brine, and dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo, leaving a bilayered liquid. The lower portion was separated (28.8 g) and identified as the desired product.

^{1}H NMR ($CDCl_3$) δ 2.4 (m, 4H), 2.0 (m, 4H) ppm.

(b) 5-Cyanocyclopentyl tetrazole

The compound obtained in (a) above (9.8 g; 0.082 moles) was dissolved in dioxane (240 mL) and treated with tri-n-butyltin azide (27.3 g; 0.082 moles) in one portion. The solution was refluxed overnight, cooled, and the dioxane removed in vacuo. The resulting liquid was taken up in ethyl ether and continuously treated with gaseous HCl for over 15 minutes. The ethereal solution was concentrated in vacuo leaving a viscous orange syrup. Yield: 11.0 g.

(c) 5-Cyanocyclopentyl-2-dodecyl-2H-tetrazole

The tetrazole (b) obtained above (11.0 g; 0.067 moles) was dissolved in acetonitrile (150 mL) containing one equivalent of triethylamine (6.8 g; 0.067 moles). The solution was heated to reflux followed by the addition of 1-bromo dodecane (16.8 g; 0.067 moles). Isolation of the 2-isomer was achieved employing the same conditions described for Example 11. Yield: 7.5 g; colorless liquid. ^{1}H NMR ($CDCl_3$) δ 4.6 (t, 2H), 2.5 (m, 4H), 2.0 (m, 6H), 1.3 (s, 18H), 0.9 (t, 3H) ppm.

(d) 2-Dodecyl-α,α-spirocyclopentyl-2H-tetrazole-5-acetic acid

The nitrile obtained in (c) above (7.5 g; 0.022 moles) was dissolved in absolute ethanol (150 mL) and treated with aqueous (50%) sodium hydroxide (18 g; 0.022 moles). The solution was refluxed for 4 hours, cooled to room temperature, and then concentration of the solvent in vacuo. The sodium salt was dissolved in H_2O, acidified to a pH of 1.0, and then the product was extracted with ethyl ether. The organic solution was dried over magnesium sulfate, filtered, and concentration of the solvent in

vacuo leaving a viscous liquid which gradually solidified over several days. Yield: 5.8 g. ^{1}H NMR ($CDCl_3$) δ 4.6 (t, 2H), 2.5 (m, 4H), 2.0 (m, 2H), 1.8 (m, 4H), 1.3 (s, 18H), 0.9 (t, 3H) ppm.

(e) 2-Dodecyl-α,α-spirocyclopentyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

The acid obtained in (d) above (1.5 g; 0.0042 moles) was dissolved in dichloromethane (50 mL), cooled to -10°C, and then treated with 2,4,6-trimethoxyaniline hydrochloride (0.94 g; 0.0042 moles). Soon after, triethylamine (0.43 g; 0.0042 moles) was added and then dicyclohexyl-carbodiimide (0.88 g; 0.0042 moles) in one portion. This suspension gradually warmed to room temperature with stirring for overnight. The mixture was filtered and the filtrate was washed with aqueous HCl (1N), brine, dried over magnesium sulfate, and then filtered. Concentration of the solvent in vacuo afforded a viscous liquid that was dissolved in 50% ethyl acetate/50% hexane and purified by silica gel chromatography. Yield: 1.6 g colorless liquid. ^{1}H NMR ($CDCl_3$) δ 7.3 (bs, 1H), 6.1 (s, 2H), 4.6 (t, 2H), 3.8 (d, 9H), 2.6 (m, 2H), 2.5 (m, 2H), 2.0 (m, 2H), 1.9 (m, 2H), 1.6 (m, 2H), 1.2 (s, 18H), 0.9 (t, 3H) ppm.

EXAMPLE 30

(±) N-(1,1-dimethylethyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide

When in the procedure of Example 13(e) an appropriate amount of tert-butylamine was substituted for 2,4,6-trimethoxyaniline and the general procedure of Example 13(e) was followed, the title compound was obtained.

^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5H), 6.4 (bs, 1H), 5.1 (s, 1H), 4.6 (t, 2H), 2.0 (m, 2H), 1.3 (s, 18H), 1.2 (s, 9H), 0.9 (t, 3H) ppm.

EXAMPLE 31

(±)-2-Octyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

When in the procedure of Example 13(b) an appropriate amount of 1-bromooctane was substituted for 1-bromododecane and the general procedure of Example 13(b), (d), and (e) was followed, the title compound was obtained, mp 113-116°C.

EXAMPLE 32

(±) 2-Hexadecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

When in the procedure of Example 13(b) an appropriate amount of 1-bromohexadecane was substituted for 1-bromododecane and the general procedure of Example 13(b), (d), and (e) was followed, the title compound was obtained, mp 134-135°C.

EXAMPLE 33

2-Tridecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

When in the procedure of Example 27(c) an appropriate amount of 1-bromotridecane was substituted for 1-bromododecane and the general procedure of Example 27(c), (d), and (e) was followed, the title compound was obtained.

^{1}H NMR ($CDCl_3$) δ 7.5 (br.s, 1H), 6.05 (s, 2H), 4.6 (t, 2H), 3.8 (s, 3H), 3.75 (s, 6H), 1.8 (s, 6H), 1.2-1.4 (m, 22H), 0.9 (m, 3H) ppm.

EXAMPLE 34

2-Dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-propanamide

(a) A mixture of methyl 3-cyanopropanoate (27.3 g, 0.241 mol), NH_4Cl (11.5 g, 0.215 mol), and NaN_3 (13.9 g, 0.214 mol) in dimethylformamide (225 mL) was heated at 100°C for 6 hours. The mixture was allowed to cool and filtered. The filtrate was concentrated in vacuo. The residue was dissolved in H_2O (200 mL). The solution was acidified with concentrated HCl (52 mL) and extracted with EtOAc (9 x 200 mL). The extracts were washed (saturated NaCl), dried ($MgSO_4$), and concentrated in vacuo to an oil; yield 29.2 g. The oil was dissolved in CH_3CN (590 mL) and Et_3N (29.5 mL, 0.21 mol). The solution was heated to 60°C. To this solution was added in one portion 1-bromododecane (49.5 mL, 0.21 mol), and the mixture was refluxed for 50 hours. The mixture was allowed to cool and filtered. The filtrate was concentrated in vacuo to a thick suspension, and the suspension was triturated with ether (500 mL). The ether was concentrated in vacuo to an oil, and the oil was chromatographed on silica gel (470 g, 70-230 mesh) using petroleum ether-EtOAc (15:1, 15 x 900 mL and 10:1, 20 x 900 mL) as eluent. A white solid was obtained; yield 12.0 g (15%) of methyl 2-dodecyl-2H-tetrazole-5-propanoate, mp 39-42°C.

Chromatography gave a white solid; yield 8.64 g (11%) of methyl 1-dodecyl-1H-tetrazole-5-propanoate, mp 43-45°C.

(b) To a stirred, room temperature solution of KOH (2.5 g) in absolute ethanol (210 mL) was added in one portion the 2-dodecyl-2H-tetrazole ester (11.5 g, 0.0354 mol), and the resulting solution was stirred

for 3 days. The solution was concentrated in vacuo to a white solid. The solid was partitioned between 0.4 M HCl (310 mL) and CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated in vacuo to a white solid; yield: 10.63 g (96.6%) of 2-dodecyl-2H-tetrazole-5-propanoic acid, mp 63-65°C.

(c) To a stirred, room temperature solution of the 2-dodecyl-2H-tetrazole acid (1.60 g, 0.00515 mol) in tetrahydrofuran (50 mL) was added in one portion carbonyldiimidazole (0.93 g, 0.0057 mol), and the mixture was stirred for 2 hours. To the mixture was added a solution of 2,4,6-trimethoxyaniline (0.99 g, 0.0054 mol) in THF (50 mL), and the mixture was refluxed for 3 days. The mixture was concentrated in vacuo to a viscous liquid that was chromatographed on silica gel (400 g, 70-230 mesh) using petroleum ether-ETOAc (1:1, 11 x 500 mL; 2:3, 18 x 500 mL) as eluent. The product was rechromatographed on silica gel (300 g, 70-230 mesh) using petroleum ether-acetone (3:1, 13 x 500 mL) as eluent to give an off-white solid; yield: 1.2 g (49%) of N-(2,4,6-trimethoxyphenyl)-2-dodecyl-2H-tetrazole-5-propanamide, mp 86-88°C.

EXAMPLE 35

N-(2,6-Bis(1-methylethyl)phenyl)-2-dodecyl-2H-tetrazole-5-propanamide

In a manner similar to Example 34, 2-dodecyl-2H-tetrazole-5-propanoic acid was condensed with 2,6-bis(1-methylethyl)aniline to give the title compound, mp 41-43°C.

EXAMPLE 36

N-(2,4-Difluorophenyl)-2-dodecyl-2H-tetrazole-5-propanamide

In a manner similar to Example 34, 2-dodecyl-2H-tetrazole-5-propanoic acid was condensed with 2,4-difluoroaniline to give the title compound, mp 86-87°C.

EXAMPLE 37

1-Dodecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-5-propanamide

In a manner similar to Example 34, methyl 1-dodecyl-1H-tetrazole-5-propanoate was saponified with KOH to give 1-dodecyl-1H-tetrazole-5-propanoic acid. The acid was condensed with 2,4,6-trimethoxy-aniline to give the title compound, mp 57-61°C.

EXAMPLE 38

(±)-2-Dodecyl-α-(2-pyridyl)-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide hydrochloride

(a) 5-(2-Pyridylmethyl)-1H-tetrazole

2-Pyridylacetonitrile (10.0 g; 0.084 moles) was dissolved in p-dioxane (200 mL) and then treated with tributyltin azide (30.9 g; 0.093 moles) in one portion. The solution was refluxed for 20 hours, cooled to room temperature, and then concentrated in vacuo. The viscous syrup was taken up in ethyl ether and treated with gaseous HCl for over 15 minutes, affording a maroon-colored precipitate that was recrystallized from ethanol. Yield: 9.1 g (55%). ^{1}H NMR (DMSO): δ 10.4 (bs, 1H), 8.9 (d, 1H), 8.4 (t, 1H), 7.9 (t, 2H), 4.8 (s, 2H) ppm.

(b) 4-(2-Pyridylmethyl)-2-dodecyl-2H-tetrazole

The tetrazole (a) (3.0 g; 0.015 moles) was taken up in acetonitrile (50 mL) containing two equivalents

of triethylamine (3.0 g; 0.030 moles). The suspension was heated to reflux and then treated with 1-bromododecane (3.7 g; 0.015 moles) dropwise for several minutes. The solution was refluxed for 16 hours, cooled to room temperature, and the solvent removed in vacuo. The residue was triturated with ethyl acetate, filtered, and concentration of the filtrate in vacuo leaving a maroon-colored liquid. The 2-isomer was obtained by dissolving the crude product in 50% hexane/50% ethyl acetate and removing the impurities, including the 1-regioisomer, by silica gel chromatography. Yield: 2.0 g (41%).
^{1}H NMR ($CDCl_3$): δ 8.5 (d, 1H), 7.7 (t, 1H), 7.3 (d, 1H), 7.2 (m, 1H), 4.5 (t, 2H), 4.4 (s, 2H), 1.9 M, 2H), 1.3 (s, 18H), 0.9 (t, 3H) ppm.

(c) (±)-2-Dodecyl-α-(2-pyridyl)-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide-HCl

Compound (b) (2.0 g; 6.0 mmoles) was dissolved in dry tetrahydrofuran (40 mL), cooled to -20°C, and then treated with n-butyllithium (4.0 mL; 6.0 mmoles) dropwise for over 5 minutes. The bright yellow solution was stirred at -20°C for 10 minutes before adding 2,4,6-trimethoxyphenyl isocyanate (1.3 g; 6.5 mmoles) in one portion. The solution gradually warmed to room temperature for over 3 hours and was then quenched with water. The product was extracted with several portions of chloroform, which were combined, dried over $MgSO_4$, and filtered. The solution was concentrated in vacuo, leaving a viscous yellow syrup that was purified by silica gel chromatography employing a gradient elution composed of hexane/ethyl acetate. The purified product was dissolved in ethyl ether and added dropwise to an ethereal HCl solution. The ether was removed in vacuo leaving a tan-colored solid. Yield: 1.8 g (51).

^{1}H NMR (DMSO): δ 9.4 (s, 1H), 8.7 (d, 1H), 8.3 (t, 1H), 7.9 (d, 1H), 7.7 (t, 1H), 6.2 (s, 2H), 5.9 (s, 1H), 4.7 (t, 2H), 3.7 (d, 9H), 1.9 (m, 2H), 1.2 (s, 18H), 0.9 (t, 3H) ppm.

EXAMPLE 39

4-Amino-1,3,5-trimethylpyrazole

(a) (1,3,5-Trimethylpyrazole

2,4-Pentanedione (3.8 g; 0.038 moles) was dissolved in acetic acid (30 mL) and then treated with methyl hydrazine sulfate (5.9 g; 0.041 moles) and sodium acetate (3.36 g; 0.041 moles). The suspension was heated on a steam bath for 2 hours, cooled to room temperature, and then added dropwise to saturated aqueous potassium carbonate. The product was extracted with two portions of ethyl acetate and the extracts were combined, dried over magnesium sulfate, and filtered. The filtrate was concentrated in vacuo, leaving an orange liquid. Yield: 3.4 g (81%). ^{1}H NMR ($CDCl_3$) δ 5.7 (s, 1H), 3.7 (s, 3H), 2.2 (s, 6H) ppm.

(b) 4-Nitro-1,3,5-trimethylpyrazole

The pyrazole from (a) above (3.1 g; 0.028, moles) was dissolved in cold sulfuric acid (15 mL), cooled to 0°C, and then treated with fuming nitric acid (12 mL). The acidic solution was heated on a steam bath for 2 hours, cooled to room temperature, and poured over ice. The solution was made basic (pH = 12) and the precipitate was collected by filtration and washed with water. Yield: 2.3 g (53%), white solid. ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 3H), 2.6 (s, 3H), 2.5 (s, 3H) ppm.

(c) 4-Amino-1,3,5-trimethylpyrazole

The compounds from (b) above (2.3 g; 0.014 moles) was catalytically hydrogenated using Raney nickel

(1 g) in methanolic ammonia (100 mL) under a hydrogen atmosphere at 50 psi. The catalyst was filtered and the solution concentrated in vacuo, leaving a residue that was triturated several times with ethyl ether. The decanted solvent was concentrated to dryness, leaving a pale red solid. Yield: 1.3 g (70%). ^1H NMR ($CDCl_3$) δ 3.6 (s, 3H), 2.4 (bs, 2H), 2.1 (s, 6H) ppm.

EXAMPLE 40

Following the general procedure of Example 39 only substituting 2-pyridylhydrazine for methylhydrazine sulfate, the following compound was obtained:

2-[4-amino-3,5-dimethyl-1H-pyrazol-1-yl]pyridine. ^1H NMR ($CDCl_3$) δ 8.4 (d, 1H), 7.7 (m, 2H), 7.2 (m, 1H), 2.4 (s, 3H), 2.2 (s, 3H), 2.0 (bs, 2H) ppm.

EXAMPLE 41

Following the general procedure of Example 13 only substituting the compound of Example 40 for 2,4,6-trimethoxyaniline in Step (e) of Example 13 the following compound was obtained:

(±)2-dodecyl-α-phenyl-N-[[1-(2-pyridyl)-3,5-dimethyl]pyrazol-4-yl]-2H-tetrazole-5-acetamide. ^1H NMR ($CDCl_3$) δ 8.3 (d, 1H), 7.8 (bs, 1H), 7.7 (d, 2H), 7.5 (d, 2H), 7.3 (m, 3H), 7.1 (t, 1H), 5.4 (s, 1H), 4.6 (5, 2H), 2.4 (s, 3H), 2.1 (s, 3H), 2.0 (m, 2H), 1.3 (s, 18H), 0.9 (t, 3H) ppm.

EXAMPLE 42

The following compound is prepared according to the procedure set forth in Chart VII:

2-dodecyl-N-(2,4,6-trimethoxphenyl)-2H-tetrazole-5-(3,3-dimethylpropanamide).

EXAMPLE 43

Isolation of the pure enantiomers of (±) 2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

A chromatographic charge is prepared by completely dissolving 1.85 g of racemic 2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, Example 13, in 45 mL of a solution of 80:20 2-propanol:hexane and warming to 65°C. Two milliliters of this solution is injected onto a 500 x 20.0 mm Chiralcel OG® preparative column (Diacel Chemical Industries, Tokyo, Japan). This charge is chromatographed over the support with 80:20 hexane:2-propanol at a flow rate of 8.0 mL/min. The column and injector are jacketed in an Advanced Air Oven (Kariba Instruments Cardiff, South Wales, UK) at a constant temperature of 40°C. The eluate is monitored by measuring its ultraviolet absorbance at 290 nm.

The first major ultraviolet absorbing fraction is the (-) enantiomer, (-)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide. The capacitance Factor k′ for this enantiomer is approximately 5.6 (112 mL solution) and the solution is designated as "Solution A". The value for the capacitance Factor k′ is given by the expression $k' = (V_e - V_o)/V_o$ where V_o is the void volume, 90 mL, and V_e is the volume of mobile phase eluted at the maximum ultraviolet absorbance of the first (-) enantiomer, i.e., (-)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide. The second major ultraviolet absorbing fraction is the (+) enantiomer, (+)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide. This component elutes at a k′ of 7.3 (208 mL solution) and

is designated as "Solution B". An intermediate fraction eluting at a k' of 6.7 (48 mL solution), which corresponds to the ultraviolet minimum between the two enantiomers contains approximately equal parts of each enantiomer.

This preparative procedure is repeated an additional 19 times. All the "Solution A" fractions are combined and concentrated to a dried film in an open beaker. This film is scraped from the sides of the beaker. The solid is collected and weighed. The resulting 708 mg of (-)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, is found to be 98% enantiomerically pure by high performance liquid chromatography using the conditions listed in Table A. The 20 fractions labeled "Solution B" are combined and dried as described for the "Solution A" fractions. The resulting 727 mg of solid, (+)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, is found to be 96% enantiomerically pure by high performance liquid chromatography using the system described in Table A. The physical properties of (-)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide and (+)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide appear in Table B.

TABLE A

Column: Chiralcel OG 4.6 x 250 mm 10 μm spherical particles
Mobile Phase: 80:20 hexane:2-propanol
Detection: 214 nm
Temperature: 40°C
Injection Volume: 20 μL
Charge Conc.: 0.150 mg/mL in the mobile phase

TABLE B

	(-)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide	(+)-2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide
Optical Rotation	$[\alpha]_D$ = -58.0 (c. 1.00 MeOH)	$[\alpha]_D$ = +55.1 (c. 1.00 MeOH)
Retention Volume	16.2 mL	18.8 mL

EXAMPLE 44

(±)-2-Dodecyl-α-methyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide

(a) (±)-2-Dodecyl-α-methyl-α-phenyl-2H-tetrazole-5-acetic acid

To a THF solution (30 mL) of n-BuLi (0.0055 mol, 1.6 M in hexanes) at -78°C under N_2 with stirring was added 1.0 g (0.00027 mol) of (±)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetic acid (Compound d, Example 13). The resulting yellow solution was stirred at -78°C for 30 minutes before iodomethane (0.34 mL, 0.0055 mol) was added. This solution was stirred for 3 hours before quenching with 1N HCl (20 mL). The mixture was then partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 1.12 g of pure product.

^1H NMR ($CDCl_3$) δ 9.9 (br.s, 1H), 7.3 (s, 5H), 4.6 (tr, 2H), 2.2 (s, 3H), 2.1 (tr, 2H), 1.4 (s, 18H), 0.9 (m, 3H) ppm.

(b) (±)-2-Dodecyl-α-methyl-α-phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide

To a dichloromethane solution (90 mL) of compound in step (a) was added 2,4,6-trimethoxyaniline·HCl (0.64 g, 0.0029 mol) and triethylamine (0.4 mL, 0.0029 mol) at 0°C under a nitrogen atmosphere with stirring. After 40 minutes, DCC (0.63 g, 0.003 mol) was added in one portion. After 10 minutes a precipitate resulted and the resulting suspension was allowed to warm to room temperature over 72 hours. The suspension was then filtered and the organic layers washed with 1N HCl, water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (10%-20% EtOAc-Hex or eluant) on SiO_2 yielded 0.5 g of pure product.
^1H NMR ($CDCl_3$) δ 8.1 (s, 1H), 7.2-7.4 (m, 5H), 6.05 (s, 2H), 4.6 (tr, 2H), 3.8 (s, 3H), 3.75 (s, 6H), 2.1 (s, 3H), 2.0 (tr, 2H), 1.4 (s, 18H), 0.9 (m, 3H) ppm.

EXAMPLE 45

(±)-2-Dodecyl-ß-phenyl-N-(2,4-6-trimethoxyphenyl)-2H-tetrazole-5-propanamide and (±)-1-dodecyl-ß-phenyl-N-(2,4,6-trimethoxyphenyl)-^{1}H-tetrazole-5-acetamide

(a) ß-cyano-N-(2,4,6-trimethoxyphenyl)benzene propanamide

To a dichloromethane (150 mL) solution of 3-cyano-3-phenylpropionic acid (5 g, 0.0286 mol) at 0°C under a nitrogen atmosphere was added triethylamine (4 mL, 0.0286 mol) and 2,4,6-trimethoxyaniline·HCl (6.3 g, 0.0286 mol). To this solution was added DCC (6.2 g, 0.29 mol). The resulting mixture was allowed to warm to room temperature over 3 hours. This was then filtered and the filtrate partitioned between 1N HCl and dichloromethane. The organic layer was washed with

brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting solid (5.1 g) was recrystallized from dichloromethane/hexanes, mpt 157-160°C.

(b) (±)-2-Dodecyl-ß-phenyl-N-(2,4-6-trimethoxyphenyl)-2H-tetrazole-5-propanamide and (±)-1-dodecyl-ß-phenyl-N-(2,4,6-trimethoxyphenyl)-^{1}H-tetrazole-5-acetamide

To a suspension of the material from step (a) (5.1 g, 0.016 mol) in dioxane (150 mL) at room temperature was added tri-n-butyltin azide (9.36 g, 0.016 mol) under N_2 with stirring. The resulting solution was heated to reflux for 24 hours. The solution was then cooled and concentrated in vacuo. The residue was redissolved in ether and HCl gas was then passed through the solution for 30 minutes. This was then concentrated in vacuo to give ß-(1H-tetrazol-5-yl)-N-(2,4,6-trimethoxyphenyl)benzene propanamide as a white solid (2.1 g) which was used without further purification.

This was dissolved in acetonitrile (50 mL) and triethylamine (0.006 mol) and then heated to reflux. 1-Bromodecane (1.3 mL, 0.0055 mol) was added and the resulting solution heated to reflux for 24 hours. This was then cooled to room temperature and concentrated in vacuo. The residue was treated with ethyl acetate and filtered. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (90% EtOAc-Hex as eluant, SiO_2) gave 2.6 g of a 2:1 mixture of regioisomers of the title compounds.
^{1}H NMR ($CDCl_3$) δ 7.3 (m, 10H, both regioisomers), 6.1 (s, 4H), both regioisomers), 5.0 (tr, 1H, regioisomer A), 4.8 (tr, 1H, regioisomer B), 4.5 (m, 2H, regioisomer A), 4.2 (m, 2H, regioisomer B), 3.8

(s, 18H, both regioisomers), 3.5 (m, 2H, regioisomer A), 3.1 (m, 2H, regioisomer B), 2.0 (tr, 4H, both regioisomers), 1.3 (s, 36H, both regioisomers), 0.9 (m, 6H, both regioisomers) ppm.

EXAMPLE 46

N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α,α-diphenyl-2H-tetrazole-5-acetamide

(a) 5-(Diphenylmethyl-1H-tetrazole

To a dioxan solution (500 mL) of diphenylacetonitrile (25.0 g, 0.129 mol) at room temperature under a nitrogen atmosphere was added tri-n-butyltin azide. The resulting solution was heated to reflux for 8 hours. This was then concentrated in vacuo. The residue was redissolved in ether (500 mL) and then treated with HCl gas for 30 minutes. This solution was then concentrated in vacuo and the resulting white solid triturated with hexane. This was then dried in vacuo to yield 15 g (50%) of the title compound, mp 154-156°C.

(b) 5-(Diphenylmethyl-2-dodecyl-2H-tetrazole

To a solution of (a) (14.8 g, 0.063 mol) in acetonitrile (250 mL) was added triethylamine (9.6 mL, 0.069 mol) at room temperature under N_2 with stirring. This solution was then heated to reflux and 1-bromododecane (15.1 mL, 0.063 mol) was added and the resulting solution was heated to reflux for 24 hours. The solution was then concentrated in vacuo and the residue redissolved in ethyl acetate. This was then washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a mixture of both regioisomers.

These were then separated using silica gel flash chromatography (hexane as eluant) to yield 7.7 g of

the title compound as a clear oil and 5.43 g of 5-(diphenylmethyl-1-dodecyl-1H-tetrazole, mp 81-84°C. ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 10H), 5.8 (s, 1H), 4.5 (tr, 2H), 1.9 (tr, 2H), 1.3 (s, 18H), 0.9 (m, 3H) ppm.

(c) N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α,α-diphenyl-2H-tetrazole-5-acetamide

To a THF solution (30 mL) of 5-(diphenylmethyl)-2-dodecyl-2H-tetrazole (1.0 g, 0.0025 mol) at -30°C under a nitrogen atmosphere with stirring was added n-BuLi (1.62 mL, 1.6 M in hexanes, 0.0026 mol). The resulting deep-red solution was stirred for 30 minutes before a THF solution (10 mL) of 2,6-diisopropyl-phenylisocyanate (0.53 mL, 0.0024 mol) was added dropwise over 10 minutes. The resulting yellow solution was allowed to warm to room temperature over 24 hours. Water (10 mL) was then added and the solution partitioned between ethyl acetate and water. The organic extract was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a yellow oil which was flash chromatographed (5% EtOAc-Hex as eluant, SiO_2) to yield 1.16 g of the title product as a clear oil.
^{1}H NMR ($CDCl_3$) δ 9.3 (s, 1H), 7.0-7.5 (m, 13H), 4.6 (tr, 2H), 2.9 (heptet, 2H), 2.0 (tr, 2H), 1.4 (s, 18H), 1.0 (s, 6H), 1.1 (s, 6H), 0.9 (m, 3H) ppm.

The following compounds were prepared by methods described previously and referred to as a reference example:

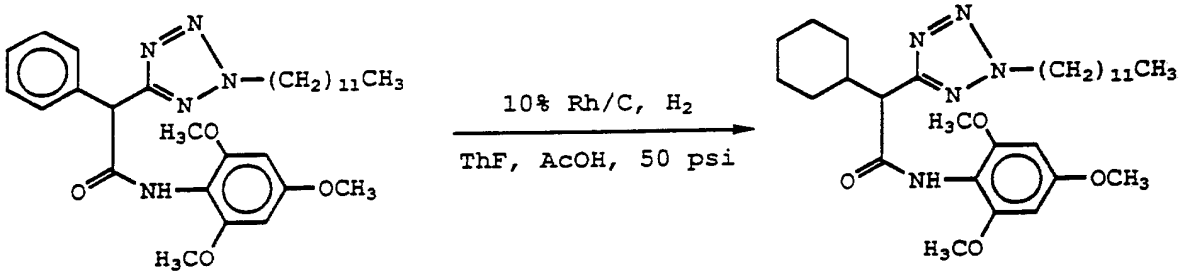
Example	Reference Example	Product
47	34	2-tetradecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-propanamide, mp 88-91°C

Example	Reference Example	Product
48	1	1-dodecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-5-acetamide, mp 108-109.5°C
49	1	2-tetradecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, mp 113-115.5°C
50	1	1-tetradecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-5-acetamide, mp 109-110°C
51	38	(±)-α-[4-dimethylamino)phenyl]-2-dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, NMR ($CDCl_3$): δ 7.4 (bs, 3H), 6.7 (bs, 2H), 6.1 (s, 2H), 5.3 (s, 1H), 4.5 (tr, 2H), 3.8 (d, 9H), 2.9 (s, 6H), 2.0 (m, 2H), 1.3 (s, 20H), 0.9 (tr, 3H) ppm.
52	38	(±)-2-Dodecyl-α-(4-fluorophenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 7.4 (bs, 3H), 6.7 (bs, 2H), 6.1 (s, 2H), 5.3 (s, 1H), 4.5 (t, 2H), 3.8 (d, 9H), 2.9 (s, 6H), 2.0 (m, 2H), 1.3 (s, 20H), 0.9 (t,3H) ppm.
53	38	(±)-2-Dodecyl-α-2-naphthalenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 8.0 (s, 1H), 7.8 (m, 4H), 7.4 (bs, 3H), 6.1 (s, 2H), 5.6 (s, 1H), 3.8 (d, 9H), 2.0 (m, 2H), 1.2 (s, 20H), 0.9 (t, 3H) ppm.
54	38	(±)-α-([1,1'-biphenyl]-4-yl)-2-dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 7.7-7.2 (m, 10H), 6.1 (s, 2H), 5.5 (s, 1H), 4.5 (t, 2H), 3.7 (d, 9H), 2.0 (m, 2H), 1.6 (bs, 2H), 1.2 (s, 18H), 0.9 (t, 3H) ppm.

Example	Reference Example	Product
55	38	(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-2-pyridinyl-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 9.2 (s, 1H), 8.6 (d, 1H), 7.8 (t, 1H), 7.6 (d, 1H), 7.3 (m, 2H), 7.1 (d, 2H), 5.6 (s, 1H), 4.6 (t, 2H), 2.9 (bs, 2H), 2.0 (m, 2H), 1.3 (s, 20H), 1.1 (d, 12H), 0.7 (t, 3H) ppm.
56	38	(±)-2-Dodecyl-α-(4-methoxyphenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide
57	38	(±)-2-Dodecyl-α-(4-methylphenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide
58	13	(±)-2-Dodecyl-α-(methyl)-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 7.4 (bs, 1H), 6.1 (s, 2H), 4.5 (t, 2H), 4.2 (q, 1H), 3.8 (d, 9H), 2.0 (m, 2H), 1.7 (d, 3H), 1.3 (s, 18H), 0.8 (tr, 3H) ppm.
59	13	(±)-2-Dodecyl-α-(phenylmethyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 7.4 (bs, 1H), 7.2 (s, 5H), 6.1 (s, 2H), 4.6 (t, 2H), 4.4 (t, 1H), 3.7 (d, 9H), 3.5 (m, 2H), 1.9 (m, 2H), 1.3 (s, 18H), 0.8 (t, 3H) ppm.

Compounds of Formula (I) containing cycloalkyl groups having from 3 to 8 carbon atoms can also be prepared employing this previously described methodology.

Alternatively, Example 13e can be catalytically hydrogenated to give the corresponding cyclohexyl analog (R_2 = cyclohexyl, R_3 = hydrogen).



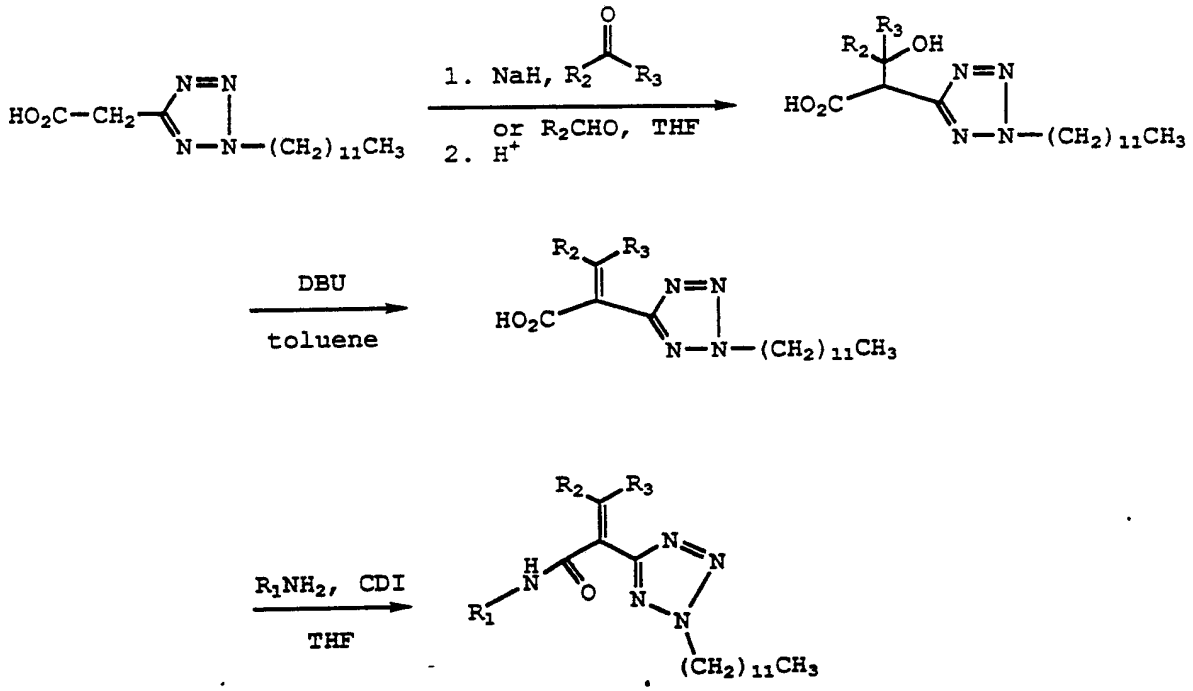
13e

Example	Product
60	(±)-2-Dodecyl-α-(cyclohexyl)-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide NMR ($CDCl_3$): δ 7.7 (s, 1H), 6.1 (s, 2H), 4.6 (t, 2H), 3.7 (d, 9H), 3.8 (d, 1H), 2.2 (m, 1H), 2.0 (m, 3H), 1.6 (m, 6H), 1.2 (s, 20H), 1.1 (m, 3H), 0.9 (t, 3H) ppm.

The following chiral analogs of Formula 13e have also been isolated.

Example	Product
61	(-)-2-Dodecyl-α-phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide $[\alpha]_D$ = -58° (1% in CH_3OH); mp 101-102°C
62	(+)-2-Dodecyl-α-phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide $[\alpha]_D$ = +55.1° (1% in CH_3OH); mp 100-101°C

Vinylic amides (11,12) are prepared from Compound 5 in Chart I as follows:

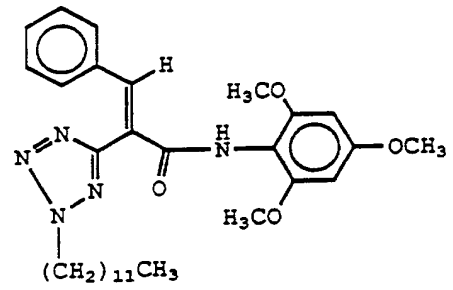


where R_1, R_2, and R_3 have been previously defined in Formula I.

Several examples are:

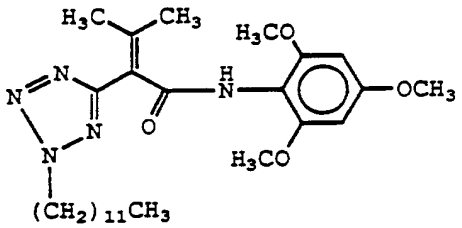
EXAMPLE 63

2-Dodecyl-α-(phenylmethylene)-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide



EXAMPLE 64

2-Dodecyl-α-(1-methylethylidene)-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide



EXAMPLE 65

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetamide

(a) 2-Dodecyl-α-hydroxy-α-phenyl-2H-tetrazole-5-acetic acid, ethyl ester

n-Butyllithium (6.9 mL of a 1.6 M hexanes solution, Aldrich) was added dropwise to a -78°C solution of tetramethylethylenediamine (1.66 mL,

11 mmole, distilled from CaH_2) in 10 mL of anhydrous THF (distilled from Na-benzophene) under dry nitrogen. The mixture was stirred for 15 minutes, then 2-dodecyltetrazole (2.38 g, 10 mmole) in anhydrous THF (5 mL) was added dropwise. The mixture was stirred for 3 hours at -78°C, then ethyl phenyl glyoxylate (1.75 mL, 11 mmole) was added dropwise. The mixture was stirred a further 2 hours, then quenched by dropwise addition of dilute HCl (pH 1). The mixture was allowed to warm to room temperature, then partitioned between ethyl acetate (200 mL) and brine (50 mL). The organic layer was dried, filtered, and concentrated to afford an oil which was flash chromatographed (silica gel, 15:1 heptane-ethyl acetate). This provided 1.55 g (37%) of the title compound as an oil. Anal. Calcd. for $C_{23}H_{36}N_4O_3$:
C, 66.32; H, 8.71; N, 13.45.
Found; C, 66.47; H, 8.52; N, 12.32.
250 MHz NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 7 Hz), 1.26 (m, 23H), 2.02 (m, 2H), 4.30 (m, 2H), 4.60 (t, 2H, J = 7 Hz), 7.38 (m, 3H), 7.66 (m, 2H), IR (film) 2928, 2856, 1735, 1449, 1256, 697 cm^{-1}.

(b) 2-Dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetic acid, ethyl ester

A solution of 2-dodecyl-α-hydroxy-α-phenyl-2H-tetrazole-5-acetic acid, ethyl ester (0.45 g, 1.08 mmole) in CH_2Cl_2 (2 mL) was added dropwise to a -78°C solution of diethyl amino sulfur trifluoride (DAST, J. Org. Chem. (40):574:578, 1975, 0.15 mL, 1.1 mmole) in CH_2Cl_2 (1 mL) under dry nitrogen. The mixture was stirred for 60 minutes at -78°C before the cooling bath was removed and the solution allowed to warm to room temperature, where it was stirred an additional 3 hours. The mixture was poured into ice water and extracted with ethyl acetate (2 x 100 mL).

The combined ethyl acetate extracts were washed with brine (50 mL) and dried. Filtration and concentration produced an oil which was flash chromatographed (silica gel, 7:1 hexane-ethyl acetate) to afford 0.3 g (66%) of the title compound as an oil.

Anal. Calcd. for $C_{23}H_{35}FN_4O_2$:
C, 66.00; H, 8.43; N, 13.39.
Found; C, 66.37; H, 8.60; N, 13.20.
IR (film) 2928, 2856, 1760, 1466, 1266, 695, 406 cm^{-1}.

(c) 2-Dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetic acid

NaOH (0.12 g, 3 mmole) was added in one portion to a stirred solution of 2-dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetic acid, ethyl ester (0.59 g, 1.4 mmole) dissolved in 6 mL of 5:1 CH_3OH-H_2O at room temperature. After stirring for 3 hours, the mixture was concentrated, diluted with H_2O, acidified with 6N HCl (pH 1) and extracted with ethyl acetate (2 x 150 mL). The combined ethyl acetate extracts were washed with brine (50 mL) and dried. Filtration and concentration afforded 0.5 g (91%) of the title compound as an oil.

(d) (±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetamide

Oxalyl chloride (0.08 mL, 0.92 mmole) was added to a stirred solution of 2-dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetic acid (0.24 g, 0.61 mmole) in 5 mL of CH_2Cl_2 at room temperature. The mixture was stirred 60 minutes, the one drop of DMF was added (immediate gas evolution). The solution was stirred overnight, concentrated (rotovap), toluene was added, and the solution concentrated again. The residue was dissolved in CH_2Cl_2 (3 mL) and added to a stirred solution of 2,6-diisopropylaniline (0.12 mL, 0.61 mmole) and Et_3N (0.14 mL, 1.0 mmole) in CH_2Cl_2

(2 mL) cooled to 0°C under dry nitrogen. After 20 minutes, the ice bath was removed and the solution allowed to warm to room temperature and stirred for 3 days. The mixture was then diluted with ethyl acetate (150 mL) and washed with dilute HCl (50 mL), bicarbonate (50 mL), brine (50 mL), and dried. Filtration and concentration afforded an oil which was flash chromatographed (silica gel, 10:1 hexanes-ethyl acetate) to produce 150 mg of the title compound as an oil which solidified on standing.

^{1}H NMR (200 MHz) 7.97 (m, 1H), 7.76 (m, 2H), 7.46 (m, 2H), 7.10 (m, 3H) 4.63 (t, 2H, J = 7 Hz), 3.03 (m, 2H), 2.05 (m, 2H), 1.25 (m, 18H), 1.10 (m, 12H), 0.88 (m, 3H) ppm.

When in the procedure of Example 65(d) an appropriate amount of 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline the following Example 66 was obtained.

EXAMPLE 66

(±)-2-Dodecyl-α-fluoro-α-phenyl-N-(2,4,6-trimethoxy phenyl)-2H-tetrazole-5-acetamide

^{1}H NMR 7.75 (m, 3H), 7.44 (m, 2H), 6.13 (s, 2H), 4.62 (t, 2H, J = 7.5 Hz), 3.80 (s, 3H), 3.76 (s, 6H), 2.04 (m, 2H), 1.25 (m, 18H), 0.88 (m, 3H) ppm,
mp 82°C-83°C.

EXAMPLE 67

Synthesis of 5-decyl-1H-tetrazole

A mixture of n-cyanodecane (20.0 g, 0.12 mol), sodium azide (8.57 g, 0.132 mol), and ammonium chloride (12.8 g, 0.24 mol) in 100 mL DMF was heated to 90°C for 72 hours. Concentrated in vacuo to one-half original volume and acidified to pH 3.0 with 1N

HCl. Concentrated again and partitioned the resulting oily white solid between ethyl acetate and water. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to give an oily solid. Triturated with ice-cold hexanes to give the title compound (15.53 g, 69%), mp 57-59°C.

EXAMPLE 68

Synthesis of 5-dodecyl-1H-tetrazole

When in the general procedure of Example 67 an appropriate amount of n-cyanododecane was substituted for n-cyanodecane, the title compound was obtained, mp 68-70°C.

EXAMPLE 69

Synthesis of 5-(diphenylmethyl)-1H-tetrazole

Tributyltin azide (51.55 g, 0.155 mol) and diphenyl acetonitrile (20.0 g, 0.103 mol) were mixed in 400 mL dioxane and heated to reflux for 20 hours. Concentrated in vacuo and redissolved the residue in ether. HCl(g) was bubbled through the solution for 1 hour and the resulting precipitate was collected and washed with hexanes to give the HCl salt of the title compound (15.88 g, 58%), mp 156-160°C.

EXAMPLE 70

Synthesis of 5-(dodecylthio)-1H-tetrazole

When in the general procedure of Example 69 an appropriate amount of n-dodecylthiocyanate was substituted for diphenyl acetonitrile, the title compound was obtained, mp 85-87°C.

EXAMPLE 71

Synthesis of ethyl(±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate

The 5-decyl-1H-tetrazole, (4.0 g, 0.019 mol), triethylamine (2.9 mL, 0.021 mol) and ethyl 2-bromophenylacetate (5.09 g, 0.021 mol) were dissolved in 200 mL acetonitrile and heated to reflux for 2 hours. Cooled and concentrated in vacuo to give a yellow oil. Chromatography to separate the regioisomers gave ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate as a clear oil (2.40 g, 34%). ^{1}H NMR ($CDCl_3$): δ 7.44-7.28 (m, 5H), 6.43 (s, 1H), 4.37-4.30 (q, 2H), 2.82-2.69 (m, 1H), 2.62-2.49 (m, 1H), 1.73-1.48 (m, 2H), 1.32-1.21 (m, 14H), and 0.90-0.85 (t, 3H) ppm.

EXAMPLE 72

Synthesis of ethyl 5-decyl-2H-tetrazole-2-acetate and ethyl 4-decyl-1H-tetrazole-1-acetate

When in the general procedure of Example 71 an appropriate amount of ethyl bromoacetate was substituted for ethyl 2-bromophenylacetate, ethyl 5-decyl-2H-tetrazole-2-acetate was obtained. ^{1}H NMR ($CDCl_3$): δ 5.37 (s, 2H), 4.31-4.23 (q, 2H), 2.94-2.88 (t, 2H), 1.82-1.74 (m, 2H), 1.40-1.22 (m, 14H), and 0.90-0.85 (t, 3H) ppm.

Also isolated the 1,5-regioisomer ethyl 5-decyl-1H-tetrazole-1-acetate. ^{1}H NMR ($CDCl_3$): δ 5.10 (s, 2H), 4.32-4.23 (q, 2H), 2.82-2.76 (t, 2H), 1.90-1.78 (m, 2H): 1.42-1.19 (m, 14H), and 0.90-0.85 (t, 3H) ppm.

EXAMPLE 73

Synthesis of ethyl (±)-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetate

When in the general procedure of Example 71 an appropriate amount of 5-(dodecylthio)-1H-tetrazole was substituted for 5-decyl-1H-tetrazole, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 7.57-7.42 (m, 5H), 6.57 (s, 1H), 4.34-4.23 (q, 2H), 3.20-3.14 (t, 2H): 1.78-1.66 (m, 2H), 1.43-1.22 (m, 14H), 0.90-0.85 (t, 3H) ppm.

EXAMPLE 74

Synthesis of ethyl(±)-5-(diphenylmethyl)-α-phenyl-2H-tetrazole-2-acetate

When in the general procedure of Example 71 an appropriate amount of 5-(diphenylmethyl)-1H-tetrazole was substituted for 5-decyl-1H-tetrazole, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 7.57-7.20 (m, 15H), 6.61 (s, 1H), 5.83 (s, 1H), 4.34-4.15 (m, 2H), 1.22-1.16 (t, 3H) ppm.

EXAMPLE 75

Synthesis of ethyl(±)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetate

When in the general procedure of Example 71 an appropriate amount of 5-dodecyl-1H-tetrazole was substituted for 5-decyl-1H-tetrazole, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 7.58-7.24 (m, 5H), 6.59 (s, 1H), 4.34-4.21 (m, 2H), 2.91-2.85 (t, 2H), 1.82-1.66 (m, 2H), 1.31-1.21 (m, 18H), 0.90-0.85 (t, 3H) ppm.

EXAMPLE 76

Synthesis of ethyl 5-dodecyl-2H-tetrazole-2-acetate

When in the general procedure of Example 71 an appropriate amount of 5-dodecyl-1H-tetrazole was substituted for 5-decyl-1H-tetrazole and an appropriate amount of ethyl bromoacetate was substituted for ethyl 2-bromophenylacetate, the title compound was obtained, mp 38-40°C.

EXAMPLE 77

Synthesis of ethyl(±)-5-dodecyl-α-pentyl-2H-tetrazole-2-acetate

When in the general procedure of Example 71 an appropriate amount of 5-dodecyl-1H-tetrazole was substituted for 5-decyl-1H-tetrazole and an appropriate amount of ethyl-2-bromoheptanoate was substituted for ethyl 2-bromophenylacetate, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 5.48-5.30 (t, 1H), 4.29-4.04 (q, 2H), 2.95-2.79 (t, 2H), 2.52-2.20 (m, 2H), 1.90-1.60 (m, 2H), 1.42-0.70 (m, 33H) ppm.

EXAMPLE 78

Synthesis of ethyl(±)-5-dodecyl-α,α-dimethyl-2H-tetrazole-2-acetate

When in the general procedure of Example 71 an appropriate amount of 5-dodecyl-1H-tetrazole was substituted for 5-decyl-1H-tetrazole and an appropriate amount of ethyl-2-bromoisobutyrate was substituted for ethyl 2-bromophenylacetate, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 4.22-4.13 (q, 2H), 2.92-2.86 (t, 2H), 2.01 (s, 6H), 1.81-1.72 (m, 2H), 1.32-1.15 (m, 18H), 0.90-0.85 (t, 3H) ppm.

EXAMPLE 79

Synthesis of (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetic acid

Solid NaOH (0.33 g, 0.0084 mol) was added to a solution of ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate in 50 mL ethanol (90%). The resulting solution was stirred for 1 hour and concentrated in vacuo. The residue was partitioned between diethyl ether and water and the aqueous layer was acidified with 1N HCl. The acidified aqueous layer was extracted with diethyl ether and this ether layer was dried over $MgSO_4$, filtered, and evaporated to give the title compound (1.78 g, 92%), mp 62-64°C.

EXAMPLE 80

Synthesis of 5-decyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl 5-decyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 83-86°C.

EXAMPLE 81

Synthesis of 5-decyl-1H-tetrazole-1-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl 5-decyl-1H-tetrazole-1-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 104-106°C.

EXAMPLE 82

Synthesis of (±)-5-(diphenylmethyl)-α-phenyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl (±)-5-(diphenylmethyl)-α-phenyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 158-161°C.

EXAMPLE 83

Synthesis of 5-dodecyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl 5-dodecyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 89-91°C.

EXAMPLE 84

Synthesis of (±)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl (±)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 76-78°C.

EXAMPLE 85

Synthesis of (±)-5-dodecyl-α-pentyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl (±)-5-dodecyl-α-pentyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 9.24 (bs, 1H), 5.54-5.48 (t, 1H), 2.94-2.88 (t, 2H), 2.54-2.30 (m, 2H), 1.81-1.75 (m, 2H), 1.30-1.25 (m, 24H), 0.90-0.86 (t, 6H) ppm.

EXAMPLE 86

Synthesis of 5-dodecyl-α,α-dimethyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl (±)-5-dodecyl-α,α-dimethyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 68-71°C.

EXAMPLE 87

Synthesis of (±)-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetic acid

When in the general procedure of Example 79 an appropriate amount of ethyl (±)-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetate was substituted for ethyl (±)-5-decyl-α-phenyl-2H-tetrazole-2-acetate, the title compound was obtained, mp 64-67°C.

EXAMPLE 88

Synthesis of N-[2,6-bis(1-methylethyl)phenyl]-5-decyl-2H-tetrazole-2-acetamide

A solution of 2,6-diisopropyl aniline (0.97 g, 0.006 mol) and 5-decyl-2H-tetrazole-2-acetic acid (1.47 g, 0.006 mol) in 100 mL dichloromethane was cooled to 0°C under an atmosphere of nitrogen. Solid DCC (1.19 g, 0.006 mol) was added in one portion and the resulting suspension was warmed to room temperature and stirred for 16 hours. Concentrated in vacuo and triturated the residue with diethyl ester. Filtered to remove the dicyclohexyl urea by-product. Concentrated the filtrate and triturated

with hexanes to give the title compound (2.02 g, 86%) as an off-white solid, mp 108-110°C.

EXAMPLE 89

Synthesis of N-[2,6-bis(1-methylethyl)phenyl]-5-decyl-1H-tetrazole-1-acetamide

When in the general procedure of Example 88 an appropriate amount of 5-decyl-1H-tetrazole-1-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid, the title compound was obtained, mp 71-73°C.

EXAMPLE 90

Synthesis of (±)-N-[2,6-bis(1-methylethyl)phenyl]-5-(diphenylmethyl)-α-phenyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-(diphenyl-methyl)-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid, the title compound was obtained, mp 180-183°C.

EXAMPLE 91

Synthesis of N-[2,6-bis(1-methylethyl)phenyl-5-dodecyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of 5-dodecyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid, the title compound was obtained, mp 91-93°C.

EXAMPLE 92

Synthesis of (±)-N-[2,6-bis(1-methylethyl)phenyl]-5-dodecyl-α-phenyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid, the title compound was obtained, mp 93-95°C.

EXAMPLE 93

Synthesis of (±)-N-[2,6-bis(1-methylethyl)phenyl]-5-dodecyl-α-pentyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-dodecyl-α-pentyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 7.53 (bs, 1H), 7.33-7.05 (m, 3H), 5.64-5.57 (t, 1H), 2.98-2.92 (t, 2H), 2.47-2.42 (m, 2H), 1.87-1.75 (m, 2H), 1.33-1.09 (m, 24H), 0.90-0.85 (t, 6H) ppm.

EXAMPLE 94

Synthesis of (±)-N-[2,6-bis(1-methylethyl)phenyl-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid, the title compound was obtained, mp 102-105°C.

EXAMPLE 95

Synthesis of (±)-5-decyl-α-phenyl-N-(2,4,6-trimethoxyphenyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-decyl-α-phenyl-2H-tetrazol-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 145-147°C.

EXAMPLE 96

Synthesis of (±)-5-(diphenylmethyl)-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-(diphenylmethyl)-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 114-117°C.

EXAMPLE 97

Synthesis of 5-dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of 5-dodecyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 144-146°C.

EXAMPLE 98

Synthesis of (±)-5-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 141-145°C.

EXAMPLE 99

Synthesis of (±)-5-dodecyl-α-pentyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-dodecyl-α-pentyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 152-155°C.

EXAMPLE 100

Synthesis of (±)-N-(2,4-difluorophenyl-5-dodecyl-α-phenyl-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-dodecyl-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4-difluoroaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 62-64°C.

EXAMPLE 101

Synthesis of N-(2,4-difluorophenyl)-5-dodecyl-2H tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of 5-dodecyl-2H-tetrazole-2-acetic

acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4-difluoroaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 103-106°C.

EXAMPLE 102

Synthesis of 5-dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of 5-dodecyl-α,α-dimethyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained.

^{1}H NMR ($CDCl_3$): δ 6.78 (bs, 1H), 6.09 (s, 2H), 3.78 (s, 3H), 3.73 (s, 6H), 2.97-2.91 (t, 2H), 2.11 (s, 6H), 1.90-1.75 (m, 2H), 1.34-1.24 (m, 18H), 0.90-0.85 (t, 3H) ppm.

EXAMPLE 103

Synthesis of (±)-5-(dodecylthio)-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide

When in the general procedure of Example 88 an appropriate amount of (±)-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetic acid was substituted for 5-decyl-2H-tetrazole-2-acetic acid and 2,4,6-trimethoxyaniline was substituted for 2,6-diisopropylaniline, the title compound was obtained, mp 141-143°C.

EXAMPLE 104

Synthesis of (±)-5-(dodecylsulfinyl)-α-phenyl-N-(2,4,6)-trimethoxyphenyl)-2H-tetrazole-2-acetamide

Solid m-chloroperbenzoic acid (0.5 g, 0.002 mol) was added in one portion to a solution of (±)-5-(dodecylthio)-α-phenyl-N-(2,4,6-trimethoxy-

phenyl)-2H-tetrazole-2-acetamide (1.15 g, 0.002 mol) in 125 mL dichloromethane at 0°C under a nitrogen atmosphere. Stirred for 3 hours and then washed with aqueous Na_2CO_3 solution, dried over $MgSO_4$, filtered, and concentrated to give a cream colored solid. Washed with solid with boiling hexanes to give the title compound (0.87 g, 74%), mp 140-143°C.

CHART I

(n = zero and $R_2 = R_3 = H$, R_1 and R_4 as defined in Formula I)

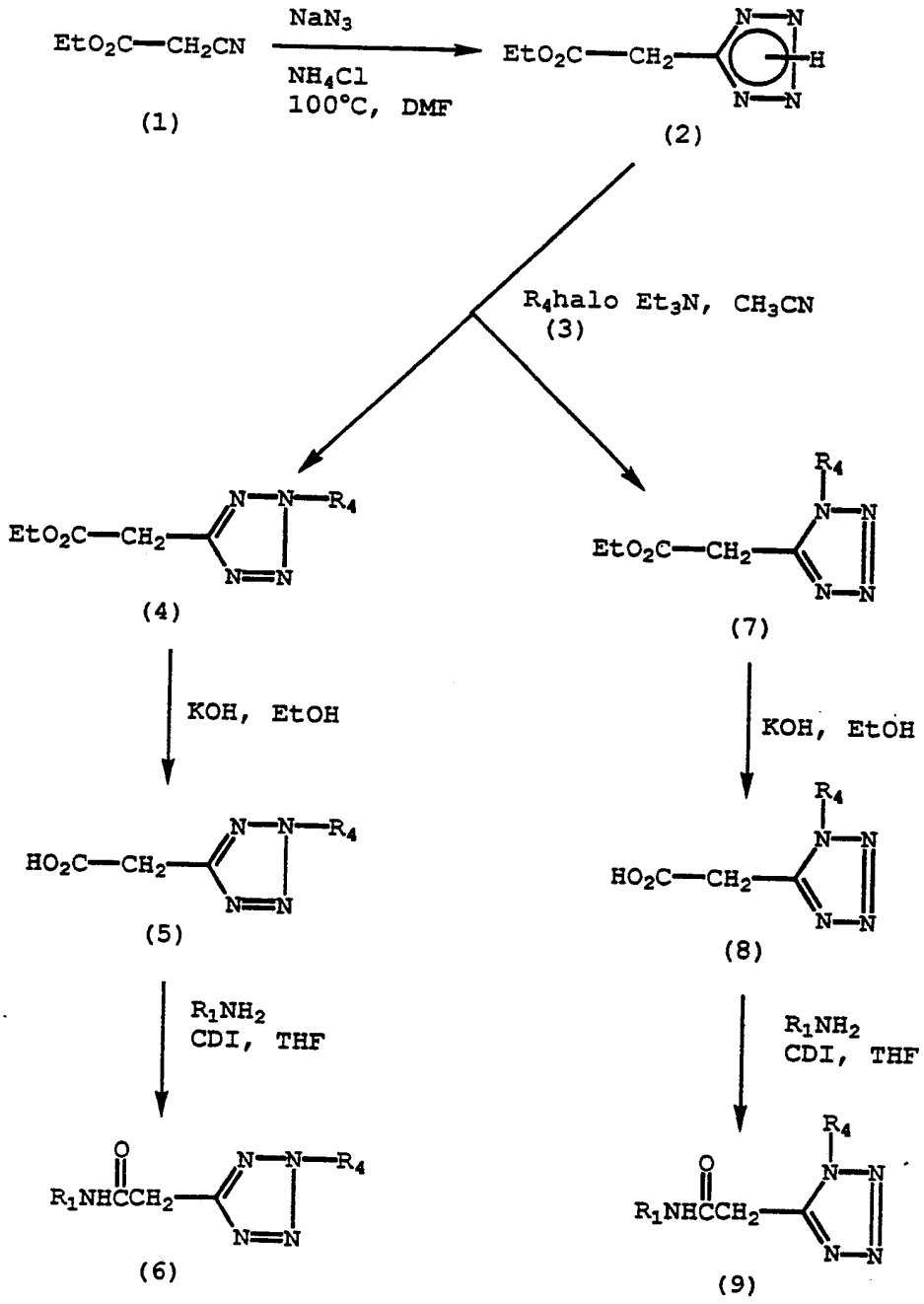


CHART II

(n = zero, R_1, R_2, R_3, and R_4 as defined in Formula I.

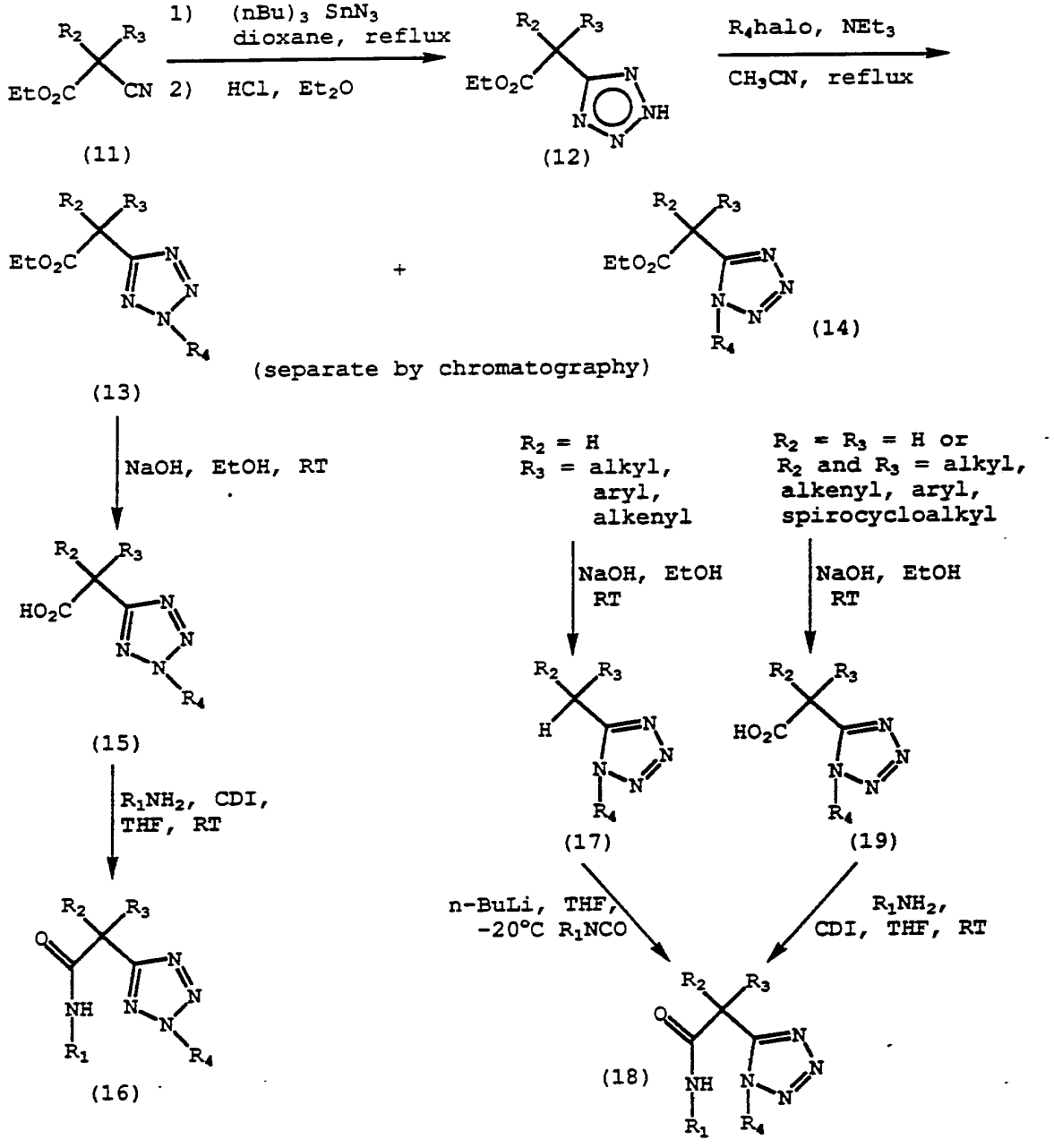


CHART II(a)

(R_2 = H, R_3 as defined in Formula I, except for aryl or heteroaryl)

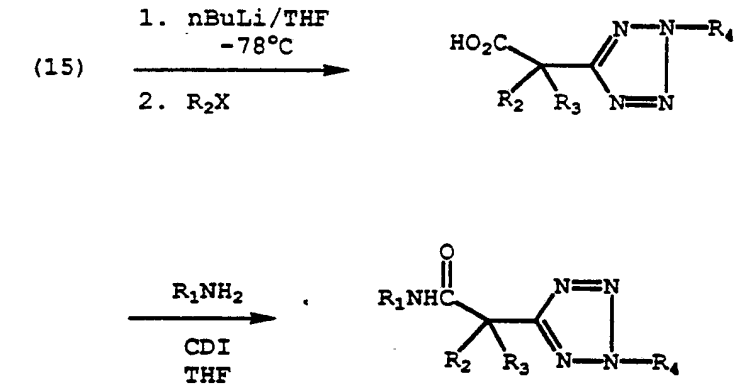


CHART III

(n = one or two, $R_2 = R_3 = H$, R_1 and R_4 as defined in Formula I)

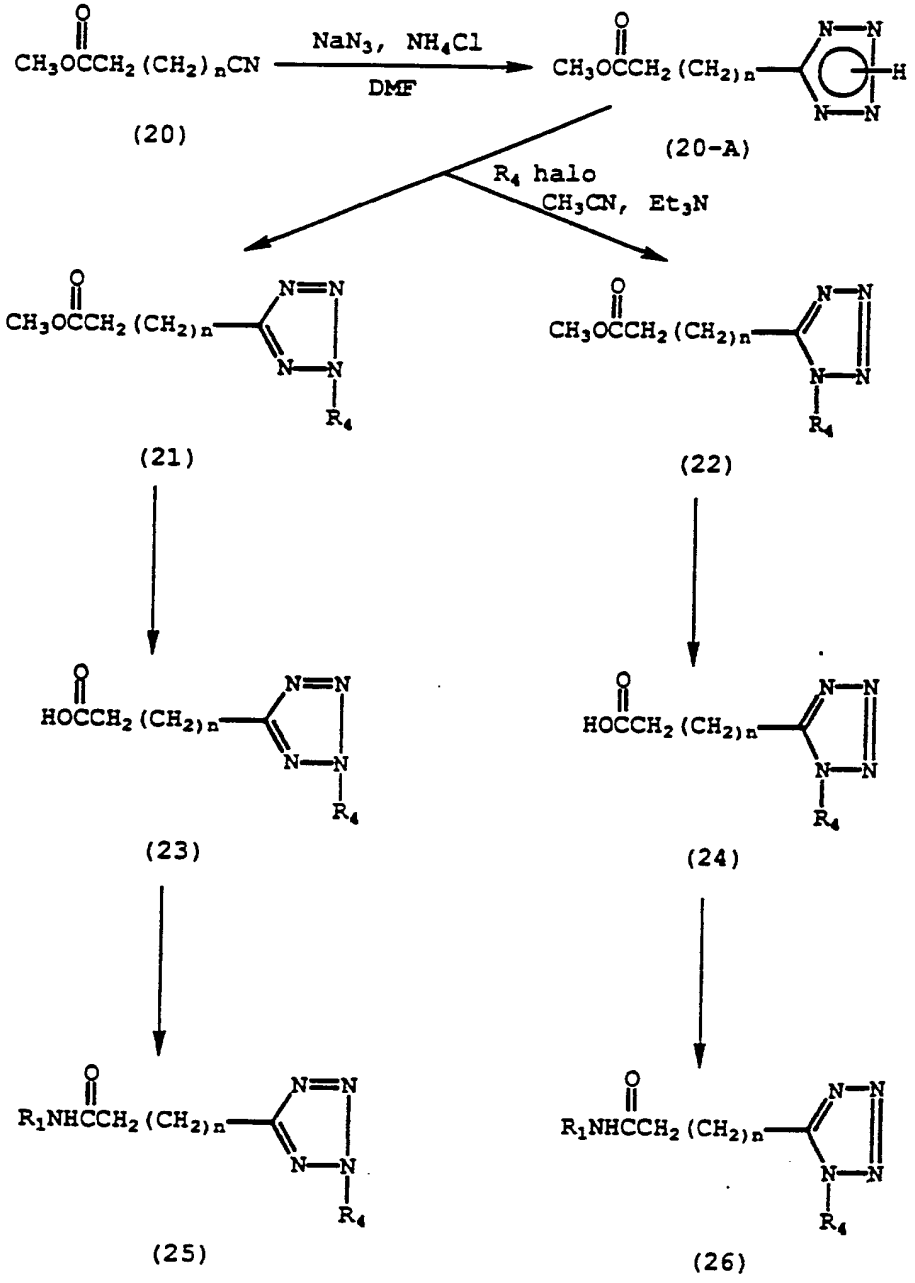


CHART IV

(n = one, R_2 = H, R_3(X) = phenyl, subt. phenyl, alkyl, alkenyl, heteroaryl and R_1 and R_4 as defined in Formula I)

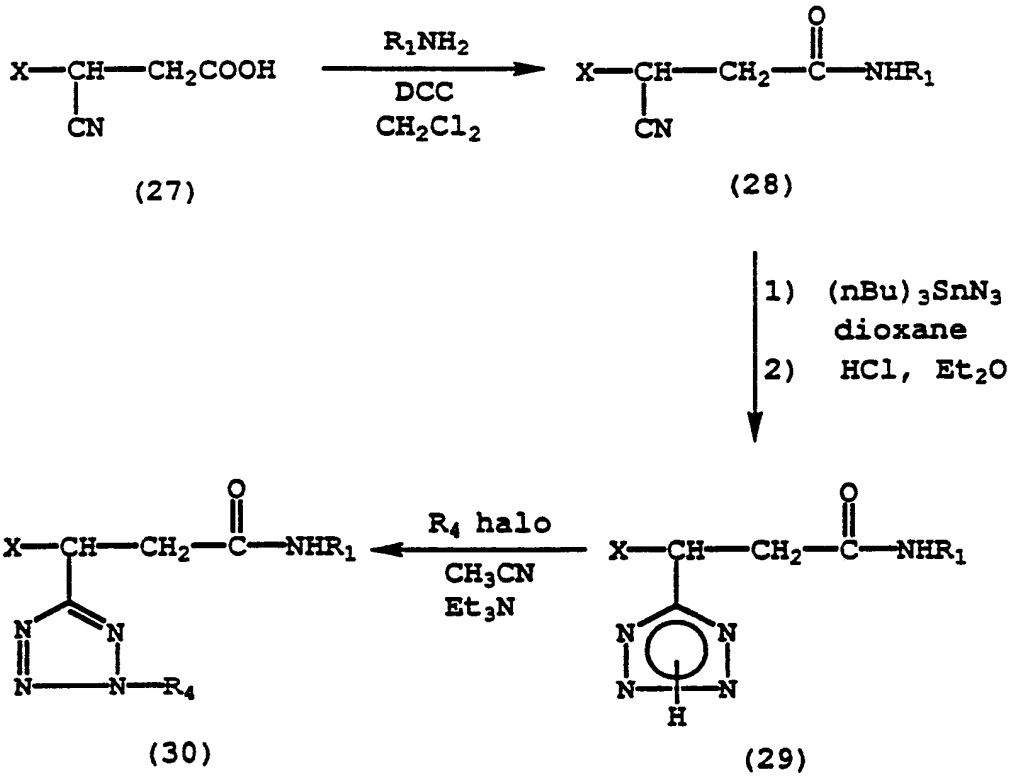


CHART V

(n = 2, R_2 = H, R_3 = phenyl or substituted phenyl, R_1 and R_4 as defined in Formula I)

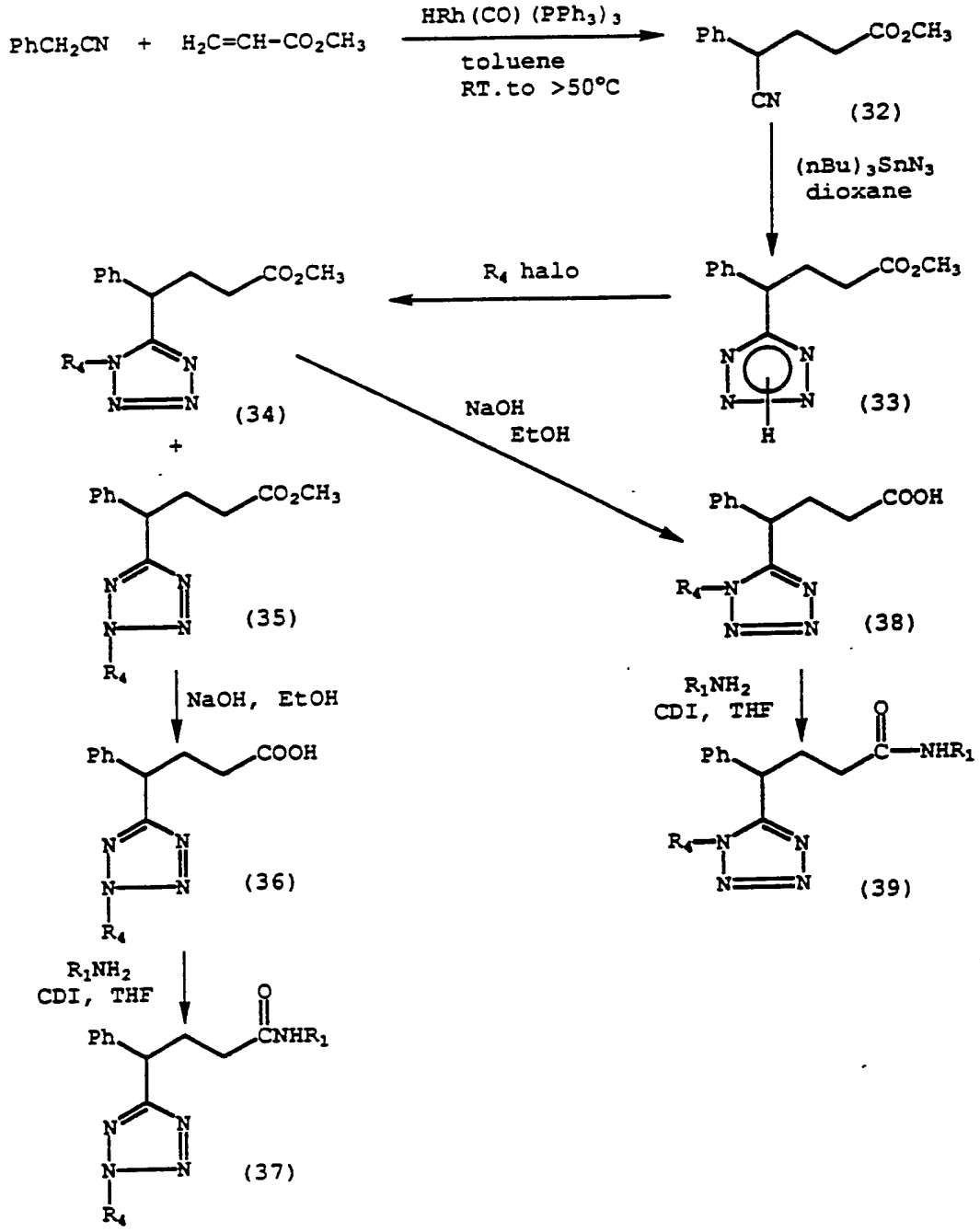


CHART VI

(n = zero, R_3 is heteroaryl, 1- or 2-naphthyl, substituted phenyl, and R_1 and R_4 are as defined in Formula I)

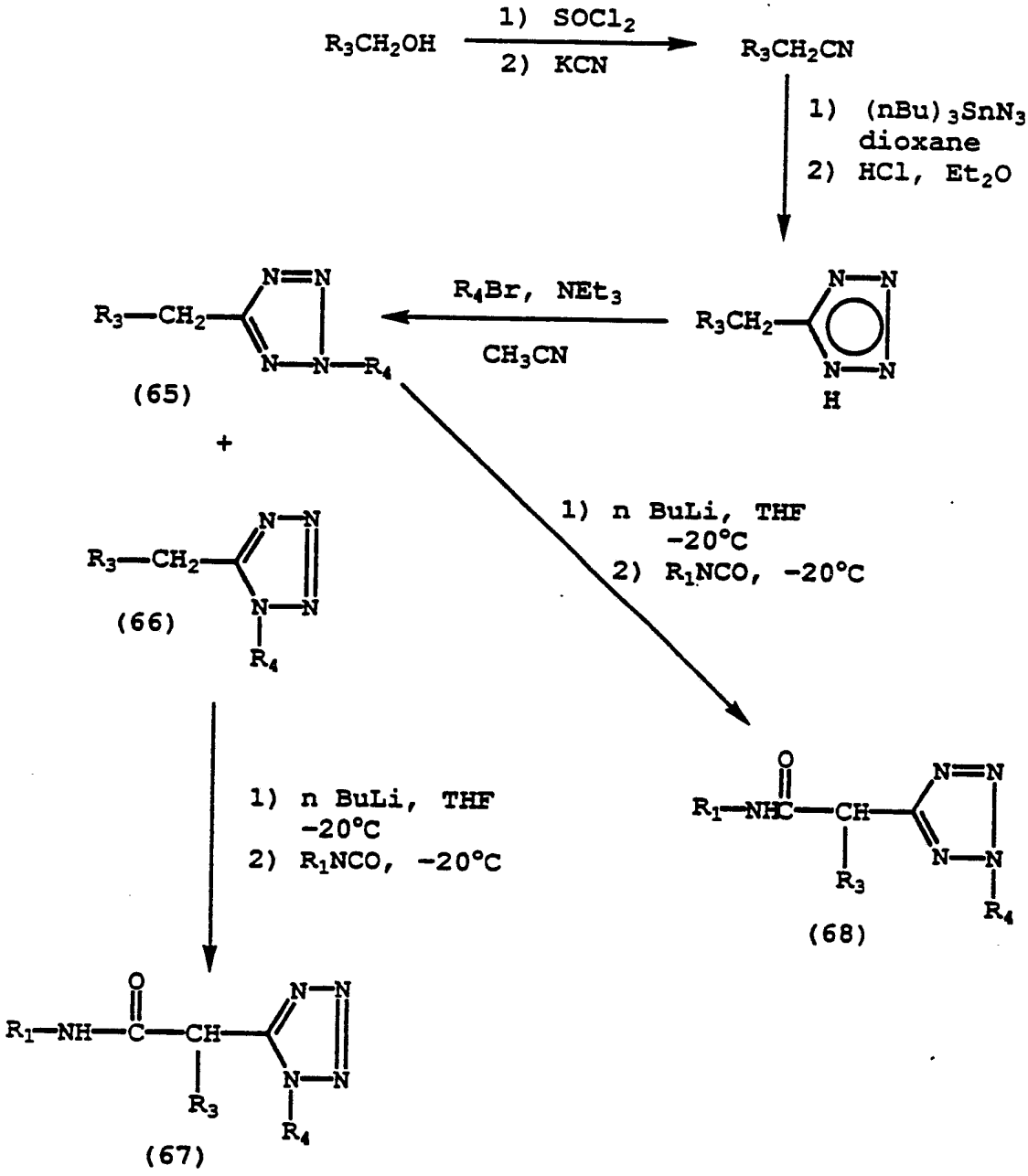


CHART VII

(n = one, R_1, R_2, R_3, and R_4 are as defined in Formula I)

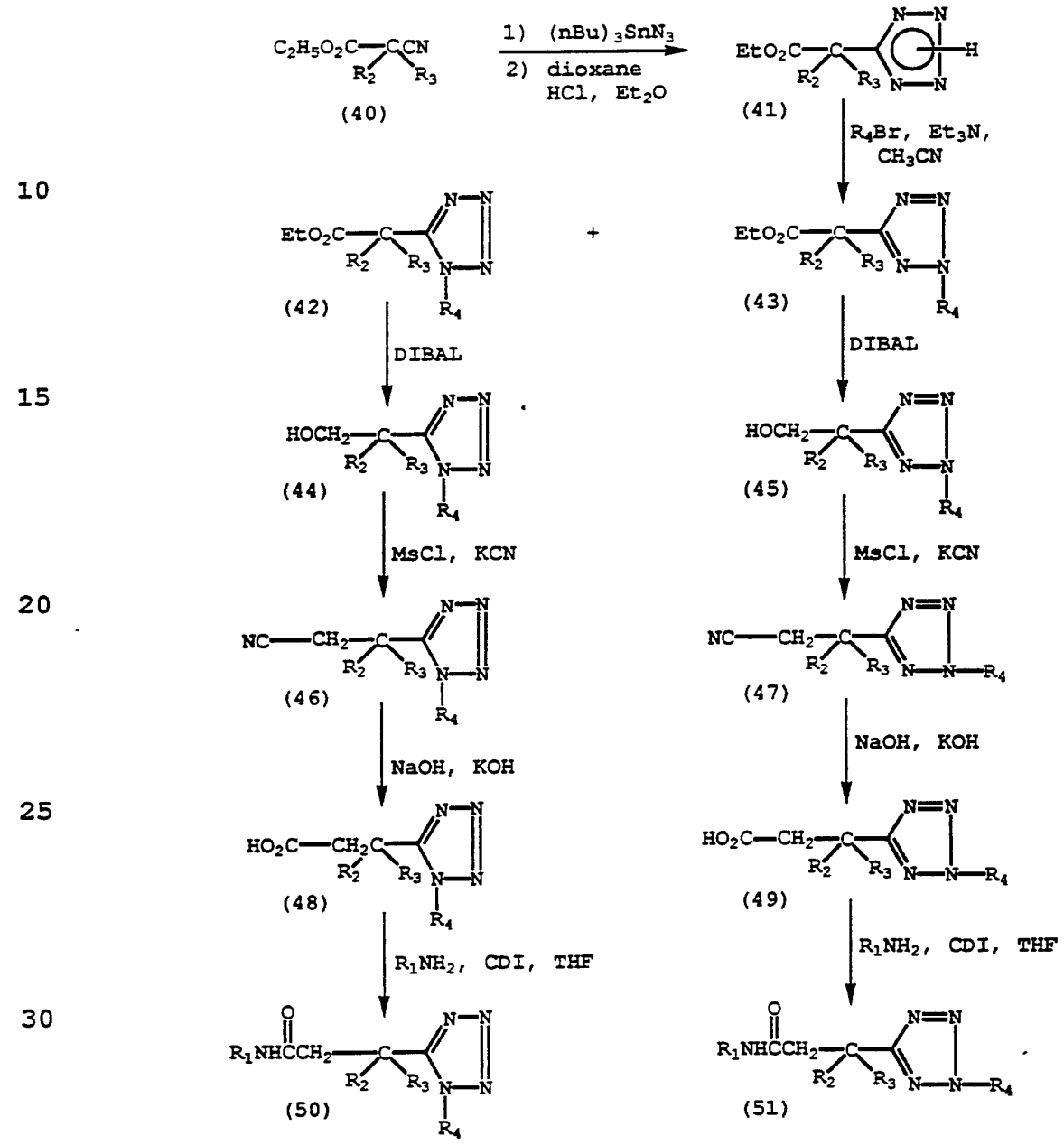


CHART VIII

(n = one, R_3 is heteroaryl and R_1, R_2, and R_4 are as defined in Formula I)

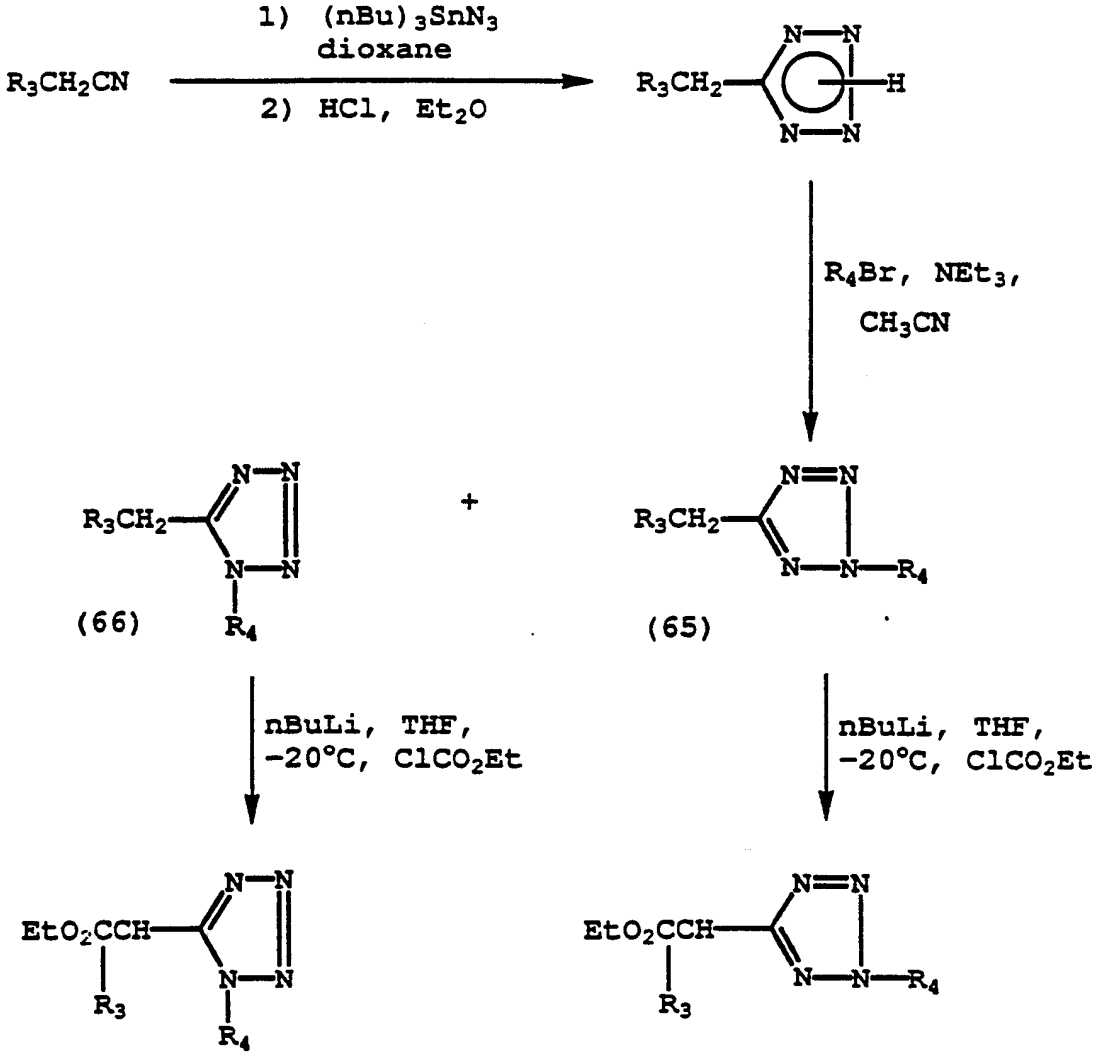


CHART IX

(n = two, R_2 and R_3 are as defined in Formula I only at least one is other than hydrogen and R_1 and R_2 are as defined in Formula I)

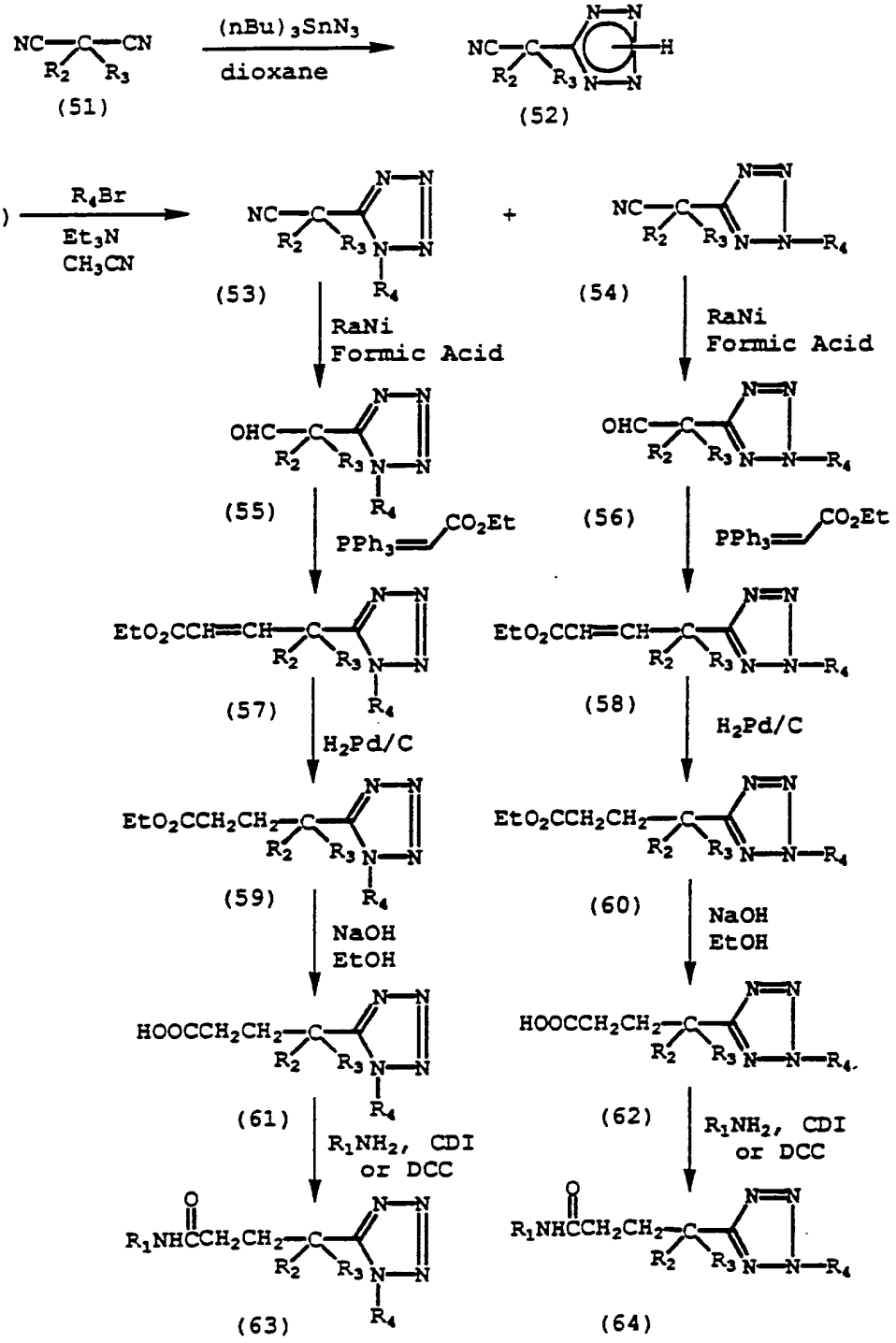


CHART X

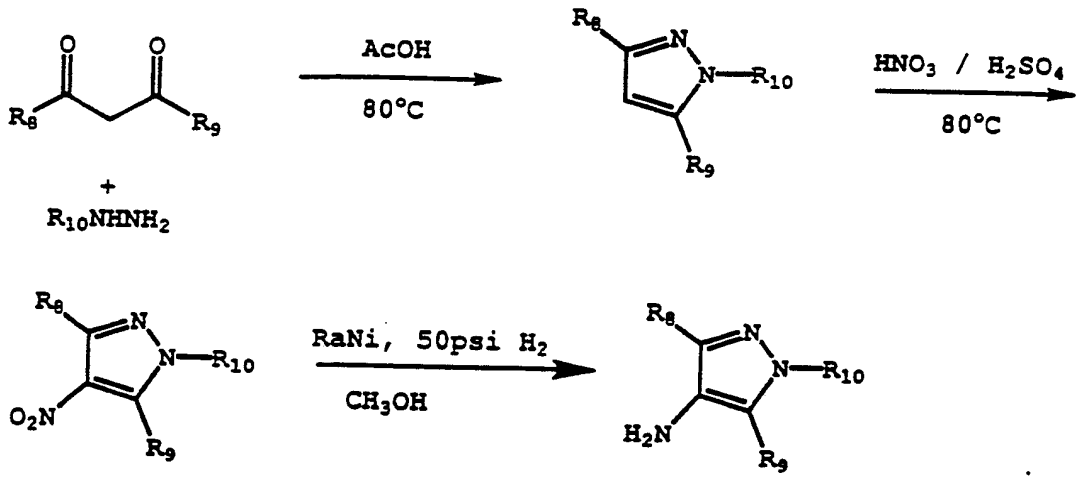


CHART XI

(n = zero, R_2, R_3 = alkyl, aryl, R_1, R_4 as defined in Formula I)

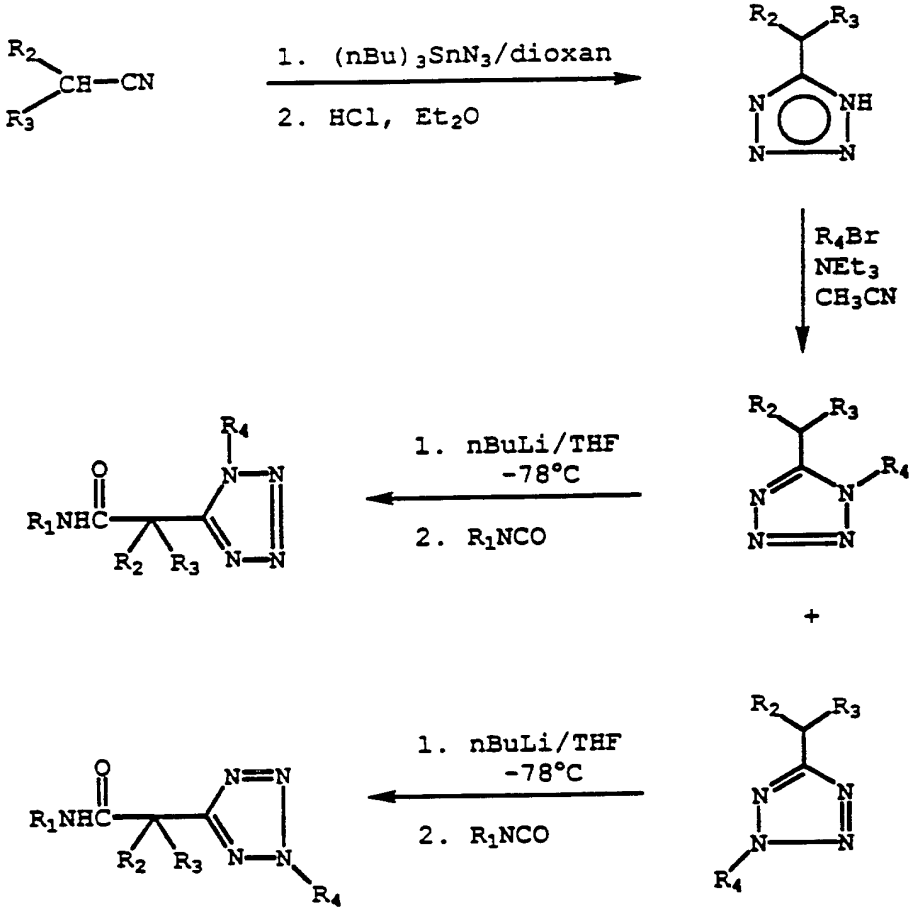


CHART XII

(R_1, R_2, and R_4 as defined in Formula I; and/or R_3 is F or OH, n is zero)

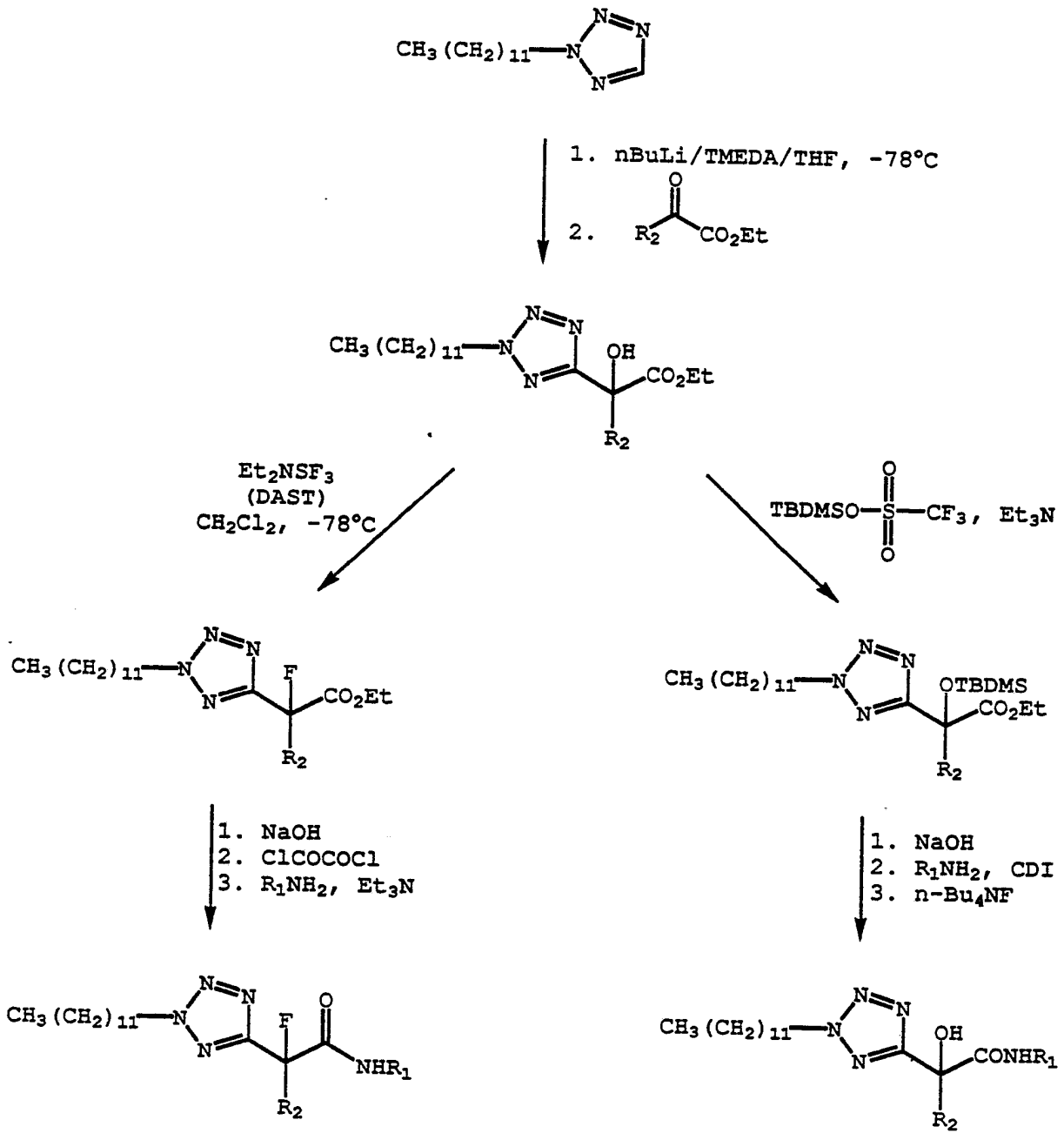
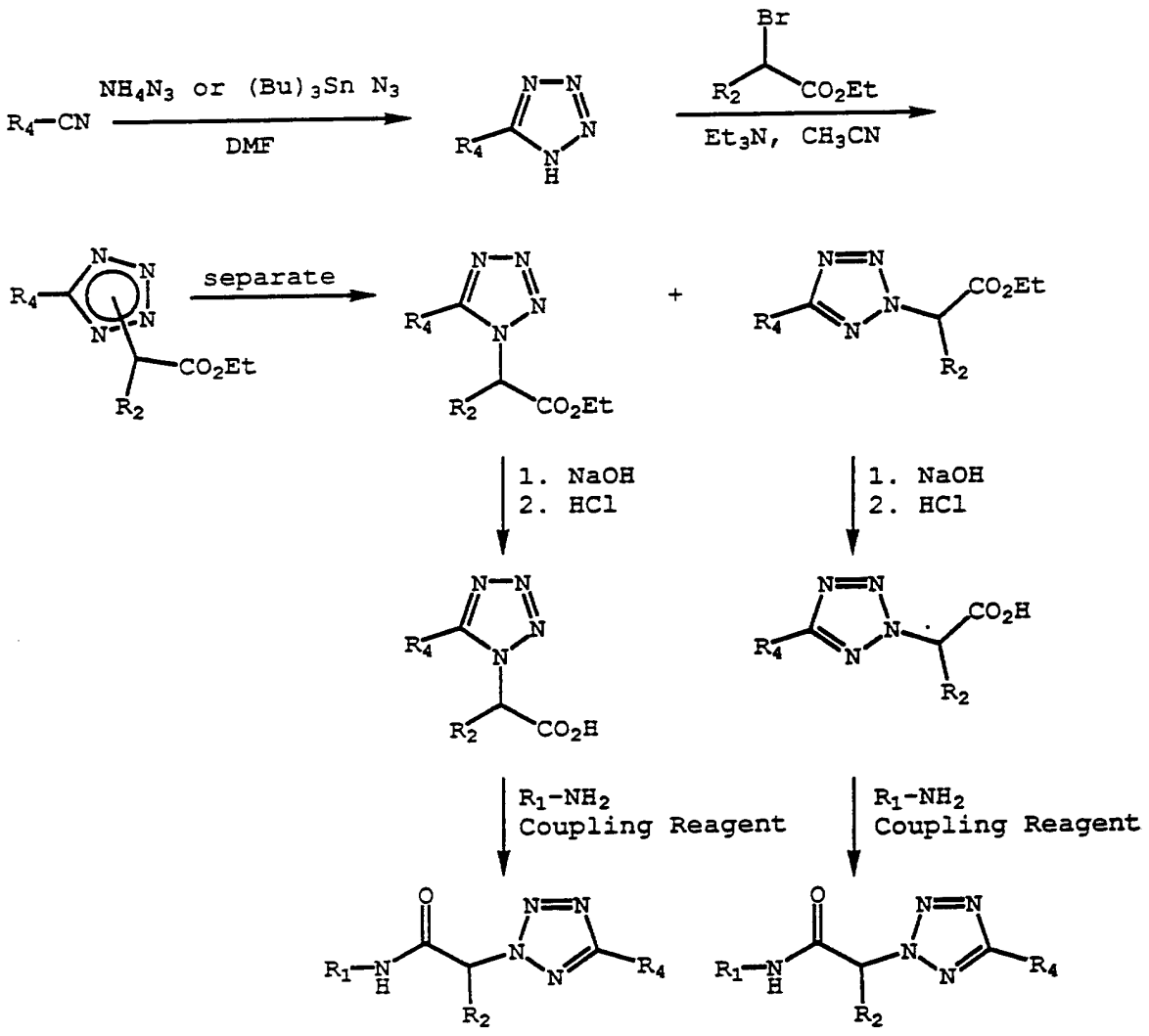


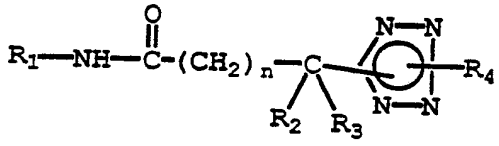
CHART XIII

(compounds of Formula I where side chain is attached to a nitrogen atom of the tetrazole ring)



CLAIMS

1. A compound of the formula



wherein n is zero, one or two;
wherein R_1 is selected from
(a) phenyl which is unsubstituted or is substituted with from one to three substituents selected from:
alkyl having from 1 to 4 carbon atoms and which is straight or branched,
alkoxy having from 1 to 3 carbon atoms and which is straight or branched,
alkylthio having from 1 to 3 carbon atoms and which is straight or branched,
hydroxy,
phenyl,
fluorine,
chlorine,
bromine,
nitro,
cyano,
trifluoromethyl,
-COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and which is straight or branched,
$-(CH_2)_mNR_5R_6$ wherein m is zero or one, and each of R_5 and R_6 is hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;

(b) 1- or 2-naphthyl which is unsubstituted or substituted with one to three substituents selected from:

alkyl having from 1 to 4 carbon atoms and which is straight or branched,

alkoxy having from 1 to 3 carbon atoms and which is straight or branched,

hydroxy,

fluorine,

chlorine,

bromine,

nitro,

cyano,

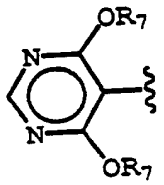
trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,

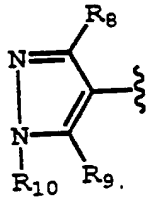
$-(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 have the meanings defined above;

(c) the group



wherein R_7 is a lower alkyl group having from 1 to 3 carbon atoms and is straight or branched;

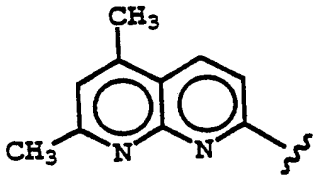
(d) the group



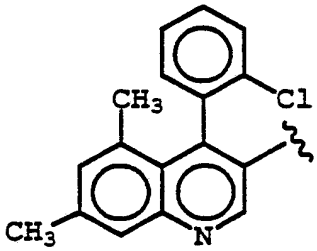
wherein R_8 and R_9 are straight or branched alkyl having from 1 to 4 carbon atoms or phenyl, and R_{10} is a straight or branched hydrocarbon group

having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or two nonadjacent double bonds; phenyl; phenyl substituted with from one to three substituents selected from straight or branched alkyl having 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 3 carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, -COOH, -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched or $(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 are as defined above; or a heterocyclic group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, or 3- or 4-pyridazinyl and the N-oxides thereof;

(e) the group



(f) the group



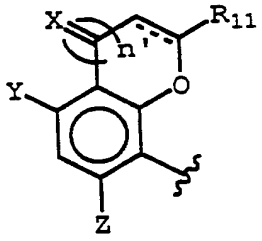
(g) a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or

is unsaturated containing one double bond or two nonadjacent double bonds;

(h) a cycloalkyl group having from 3 to 8 carbon atoms;

(i) a heteroaromatic group selected from 2-, 3-, or 4-pyridyl which is unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms or 2-, 4-, or 5-pyrimidinyl, and the N-oxides thereof;

(j) the group



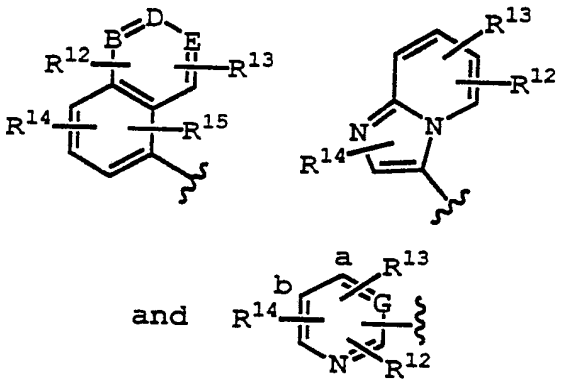
wherein --- denotes a single or double bond;

Y and Z are each independently hydrogen, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms or halo;

X is oxygen or two hydrogen atoms;

R_{11} is hydrogen or a straight or branched alkyl group of 1 to 4 carbon atoms, and n' is zero or one; or

(k) is selected from the group



and

wherein R^{12}, R^{13}, R^{14}, and R^{15} are each independently hydrogen, halo, a straight or branched alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 3 carbon atoms, and alkylthio group of 1 to 3 carbon atoms, cycloaklylthio of five to seven carbon atoms, phenylalkylthio in which alkyl is 1 to 4 carbon atoms, substituted phenylthio, heteroarylthio, or heteroaryloxy; and B, D, E, and G are nitrogen or carbon where one or more of B, D, and E is nitrogen; with the proviso that when G = nitrogen the group is attached to the nitrogen atom of formula I at the 4- or 5-position of the pyrimidine ring (a and b);

wherein R_2 and R_3 are the same or different and are selected from:

(a) hydrogen, halo or one of R_2 or R_3 is hydroxy;

(b) a straight or branched alkyl group having from 1 to 12 carbon atoms, or a cycloalkyl group having from 3 to 8 carbon atoms;

(c) a phenyl or phenylalkyl group where alkyl is from 1 to 4 carbon atoms and which the phenyl ring unsubstituted or substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, alkythio, straight or branched having 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, nitro, phenyl, or $(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 have the meanings defined above;

(d) a straight or branched alkenyl group having from 2 to 6 carbon atoms; or

(e) R_2 and R_3 taken together with the carbon atom to which they are attached form an alkylidene group of 1 to 4 carbon atoms, a benzylidene or a spiroalkyl group having from 3 to 7 carbon atoms; or

(f) when R_2 is hydrogen, F, alkyl of C_{1-12} atoms, R_3 is a heteroaryl selected from a 5- or 6-membered monocyclic or fused bicyclic heterocyclic group containing at least 1 to 4 heteroatoms in at least one ring, said heteroatoms being nitrogen, oxygen, or sulfur and combinations thereof, said heterocyclic group being unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms and the N-oxides thereof;

(g) 1- or 2-naphthyl which is unsubstituted or substituted with one to three substituents selected from:

alkyl having from 1 to 4 carbon atoms and which is straight or branched,

alkoxy having from 1 to 3 carbon atoms and which is straight or branched,

wherein R_4 is a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and is saturated or is unsaturated and has 1 double bond or has 2 nonadjacent double bonds or is alkylthio having 1 to 20 carbon atoms and is saturated; or a pharmaceutically acceptable salt or individual enantiomeric isomer thereof.

2. A compound of Claim 1 wherein R_4 is in the 2-position of the tetrazole ring and the side chain is attached to the carbon atom of the tetrazole ring.

3. A compound of Claim 2 wherein n is zero.

4. A compound of Claim 3 wherein each of R_2 and R_3 is hydrogen.

5. A compound of Claim 4 wherein R_4 is a saturated hydrocarbon chain and has from 8 to 18 carbon atoms.

6. A compound of Claim 5 wherein R_1 is phenyl or substituted phenyl.

7. A compound of Claim 6 which is

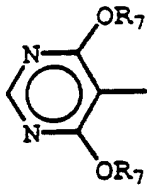
N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-2H-tetrazole-5-acetamide;

2-Dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide;

N-(2,4-Difluorophenyl)-2-dodecyl-2H-tetrazole-5-acetamide;

2-tetradecyl-N-(2,4,6-tri-methoxyphenyl)-2H-tetrazole-5-acetamide.

8. A compound of Claim 5 wherein R_1 is the group



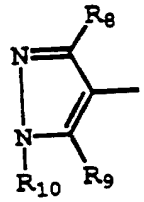
wherein R_7 is a lower alkyl group having from 1 to 3 carbon atoms and is straight or branched.

9. A compound of Claim 8 which is
N-(4,6-dimethoxy-5-pyrimidinyl)-2-dodecyl-2H-tetrazole-5-acetamide; or
N-(4,6-dimethoxy-5-pyrimidinyl)-2-dodecyl-1H-tetrazole-5-acetamide.

10. A compound of Claim 5 wherein R_1 is a heteroaromatic group selected from 2-, 3-, or 4-pyridyl which is unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms, or 2-, 4-, or 5-pyrimidinyl and the N-oxides thereof.

11. A compound of Claim 10 which is
2-dodecyl-N-(3-methyl-2-pyridinyl)-2H-tetrazole-5-acetamide.

12. A compound of Claim 5 wherein R_1 is the group



wherein R_8 and R_9 are straight or branched alkyl having from 1 to 4 carbon atoms or phenyl, and R_{10} is a straight or branched hydrocarbon group having from 1 to 18 carbon atoms which is saturated or is unsaturated containing one double bond or two nonadjacent double bonds; phenyl; phenyl substituted with from one to three substituents selected from straight or branched alkyl having 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 3 carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, -COOH, -COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched or $(CH_2)_mNR_5R_6$ wherein m, R_5, and R_6 are as defined above; or a heterocyclic group selected from 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, or 3- or 4-pyridazinyl and the N-oxides thereof.

13. A compound of Claim 12 which is
2-dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide; or
1-dodecyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-tetrazole-5-acetamide.

14. A compound of Claim 3 wherein one of R_2 and R_3 is hydrogen and the other is phenyl which is unsubstituted or substituted.

15. A compound of Claim 14 wherein R_4 is saturated hydrocarbon chain having from 8 to 18 carbon atoms.

16. A compound of Claim 15 wherein R_1 is a phenyl group which is unsubstituted or is substituted.

17. A compound of Claim 16 which is
(±) 2-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
(±) 2-dodecyl-N,α-diphenyl-2H-tetrazole-5-acetamide,
(±)-N-[2,6-bis(1-methylethyl)phenyl]-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide,
(±)-N-(2,4-difluorophenyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide,
(±)-2-octyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or
(±)-2-hexadecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.

18. A compound of Claim 15 which is
(±)-N-(4,6-dimethoxy-5-pyrimidinyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide,
(±)-N-(5,7-dimethyl-1,8-naphthyridine-2-yl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide,
(±)-2-dodecyl-α-phenyl-N-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2H-tetrazole-5-acetamide,
(±)-N-cyclopropyl-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide,
(±)-2-dodecyl-α-phenyl-N-2-pyridinyl-2H-tetrazole-5-acetamide,
(±)-2-dodecyl-N-(3-methyl-2-pyridinyl)-α-phenyl-2H-tetrazole-5-acetamide,
(±)-2-dodecyl-N-(3-methyl-2-pyridinyl)-2-phenyl-2H-tetrazole-5-acetamide, N-oxide, or
(±)-N-(1,1-dimethylethyl)-2-dodecyl-α-phenyl-2H-tetrazole-5-acetamide.

19. A compound of Claim 3 wherein R_3 is a 5- or 6-membered monocyclic or fused bicyclic heterocyclic group containing at least 1 to 4 heteroatoms in at least one ring, said heteroatom being nitrogen, oxygen, or sulfur, and combinations thereof, with said heterocyclic group being unsubstituted or substituted with an alkyl group having from 1 to 4 carbon atoms, and the N-oxides thereof.

20. A compound of Claim 19 wherein R_3 is 2-, 3-, or 4-pyridyl.

21. A compound of Claim 20 which is (±)-2-dodecyl-α-(2-pyridyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide, or

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-2-pyridinyl-2H-tetrazole-5-acetamide.

22. A compound of Claim 3 wherein each of R_2 and R_3 is other than hydrogen.

23. A compound of Claim 22 which is

2-dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,

2-dodecyl-α,α'-(2-propenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,

1-(2-dodecyl-2H-tetrazol-5-yl)-N-(2,4,6-trimethoxyphenyl)cyclopentanecarboxamide, or

2-tridecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide.

24. A compound of Claim 2 wherein n is one or two.

25. A compound of Claim 24 wherein R_1 is phenyl which is unsubstituted or which is substituted.

26. A compound of Claim 25 which is
2-dodecyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-propanamide,
N-(2,6-bis(1-methylethyl)phenyl)-2-dodecyl-2H-tetrazole-5-propanamide,
N-(2,4-difluorophenyl)-2-dodecyl-2H-tetrazole-5-propanamide, or
1-dodecyl-N-(2,4,6-trimethoxyphenyl)-1H-tetrazole-5-propanamide.

27. A compound of Claim 1 which is
(±)-n-(2,4-difluorophenyl)-1-dodecyl-α-phenyl-1H-tetrazole-5-acetamide,
(±)-N-[2,6-bis(1-methylethyl)phenyl]-1-dodecyl-α-phenyl-1H-tetrazole-5-acetamide.

28. A compound of Claim 6 wherein R_1 is 2,6-(1-methylethyl)phenyl or 2,4,6-trimethoxyphenyl; n is zero; R_2 and R_3 are each independently hydrogen, methyl, fluoro, cyclohexyl, phenyl, or substituted phenyl, phenylalkyl, or naphthyl, and R_4 is in the 2-position and has 12 carbon atoms and the side chain is attached to the carbon atom of the tetrazole ring.

29. A compound of Claim 28 which is
(±)-2-Dodecyl-α-methyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,
(±)-2-Dodecyl-α-(4-fluorophenyl)-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,

(±)-2-Dodecyl-α-2-naphthalenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,

(±)-α-([1,1'-biphenyl]-4-yl)-2-dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide,

(±)-2-Dodecyl-α-methyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide,

(±)-2-Dodecyl-α-phenylmethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-5-acetamide,

(±)-2-Dodecyl-α-cyclohexyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide,

(-)-2-Dodecyl-α-phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide $[\alpha]_D$ = -58° (1% in CH_3OH),

(+)-2-Dodecyl-α-phenyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-5-acetamide $[\alpha]_D$ = +55.1° (1% in CH_3OH),

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-dodecyl-α-fluoro-α-phenyl-2H-tetrazole-5-acetamide, or

(±)-2-Dodecyl-α-fluoro-α-phenyl-N-(2,4,6-trimethoxy phenyl)-2H-tetrazole-5-acetamide.

30. A compound of Claim 1 wherein R_4 is attached to the carbon atom of the tetrazole ring and the side chain is on the 2-position of the tetrazole ring.

31. A compound of Claim 30 which is

N-[2,6-bis(1-methylethyl)phenyl]-5-decyl-2H-tetrazole-2-acetamide;

N-[2,6-bis(1-methylethyl)phenyl-5-dodecyl-2H-tetrazole-2-acetamide;

(±)-N-[2,6-bis(1-methylethyl)phenyl]-5-dodecyl-α-phenyl-2H-tetrazole-2-acetamide;

(±)-N-[2,6-bis(1-methylethyl)phenyl]-5-dodecyl-α-pentyl-2H-tetrazole-2-acetamide;

(±)-N-[2,6-bis(1-methylethyl)phenyl-5-(dodecylthio)-α-phenyl-2H-tetrazole-2-acetamide;

(±)-5-decyl-α-phenyl-N-(2,4,6-trimethoxyphenyl-2H-tetrazole-2-acetamide;

5-dodecyl-N-(2,4,6-trimethoxy-phenyl)-2H-tetrazole-2-acetamide;

(±)-5-dodecyl-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

(±)-5-dodecyl-α-pentyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

(±)-N-(2,4-difluorophenyl-5-dodecyl-α-phenyl-2H-tetrazole-2-acetamide;

5-dodecyl-α,α-dimethyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide;

(±)-5-(dodecylthio)-α-phenyl-N-(2,4,6-trimethoxyphenyl)-2H-tetrazole-2-acetamide; or,

(±)-5-(dodecylsulfinyl)-α-phenyl-N-(2,4,6)-trimethoxyphenyl)-2H-tetrazole-2-acetamide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/06388

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D257/04; C07D403/12; C07D471/04; C07D401/12
C07D401/14; A61K31/41; A61K31/435; A61K31/495

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 035 046 (OTSUKA PHARMACEUTICAL COMPANY) 9 September 1981 see page 114 - page 115; claim 1 ---	1
P,A	WO,A,9 117 150 (WARNER-LAMBERT COMPANY) 14 November 1991 *Page 0,1,2* *Page28-34:claims* -----	1

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 OCTOBER 1992	23. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9206388 SA 63312

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0035046	09-09-81	None	
WO-A-9117150	14-11-91	US-A- 5073565	17-12-91
		AU-A- 7854491	27-11-91